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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **ENDOTHELIAL CELL EXPRESSION PATTERNS**

(57) Abstract: To gain a better understanding of tumor angiogenesis, new techniques for isolating endothelial cells (ECs) and evaluating gene expression patterns were developed. When transcripts from ECs derived from normal and malignant colorectal tissues were compared with transcripts from non-endothelial cells, over 170 genes predominantly expressed in the endothelium were identified. Comparison between normal- and tumor-derived endothelium revealed 79 differentially expressed genes, including 46 that were specifically elevated in tumor-associated endothelium. Experiments with representative genes from this group demonstrated that most were similarly expressed in the endothelium of primary lung, breast, brain, and pancreatic cancers as well as in metastatic lesions of the liver. These results demonstrate that neoplastic and normal endothelium in humans are distinct at the molecular level, and have significant implications for the development of anti-angiogenic therapies in the future.

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ENDOTHELIAL CELL EXPRESSION PATTERNS

- [01] This application claims the benefit of provisional applications serial numbers 60/222,599 filed August 2, 2000, 60/224,360 filed August 11, 2000, and 60/282,850 filed April 11, 2001, the disclosures of which are expressly incorporated herein.
- [02] The U.S. government retains certain rights in the invention by virtue of the provisions of National Institutes of Health grants CA57345 and CA43460, which supported this work.

TECHNICAL FIELD OF THE INVENTION

- [03] This invention is related to the area of angiogenesis and anti-angiogenesis. In particular, it relates to genes which are characteristically expressed in tumor endothelial and normal endothelial cells.

BACKGROUND OF THE INVENTION

- [04] It is now widely recognized that tumors require a blood supply for expansive growth. This recognition has stimulated a profusion of research on tumor angiogenesis, based on the idea that the vasculature in tumors represents a potential therapeutic target. However, several basic questions about tumor endothelium remain unanswered. For example, are vessels of tumors qualitatively different from normal vessels of the same tissue? What is the relationship of tumor endothelium to endothelium of healing wounds or other physiological or pathological forms of angiogenesis? The answers to these questions critically impact on the potential for new therapeutic approaches to inhibit angiogenesis in a specific manner.

- [05] There is a continuing need in the art to characterize the vasculature of tumors relative to normal vasculature so that any differences can be exploited for therapeutic and diagnostic benefits.
- [06] One technique which can be used to characterize gene expression, or more precisely gene transcription, is termed serial analysis of gene expression (SAGE). Briefly, the SAGE approach is a method for the rapid quantitative and qualitative analysis of mRNA transcripts based upon the isolation and analysis of short defined sequence tags (SAGE Tags) corresponding to expressed genes. Each Tag is a short nucleotide sequences (9-17 base pairs in length) from a defined position in the transcript. In the SAGE method, the Tags are dimerized to reduce bias inherent in cloning or amplification reactions. (See, US Patent 5,695,937) SAGE is particularly suited to the characterization of genes associated with vasculature stimulation or inhibition because it is capable of detecting rare sequences, evaluating large numbers of sequences at one time, and to provide a basis for the identification of previously unknown genes.

SUMMARY OF THE INVENTION

- [07] One embodiment of the invention provides an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 17, 19, and 44, as shown in SEQ ID NO: 196, 200, 212, 230, 232, and 271, respectively. The molecule can be, for example, an intact antibody molecule, a single chain variable region (ScFv), a monoclonal antibody, a humanized antibody, or a human antibody. The molecule can optionally be bound to a cytotoxic moiety, bound to a therapeutic moiety, bound to a detectable moiety, or bound to an anti-tumor agent.

[08] According to another embodiment of the invention a method of inhibiting neoangiogenesis is provided. An effective amount of an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 17, 19, 22, and 44, as shown in SEQ ID NO: 196, 200, 212, 230, 232, 238, and 271, respectively, is administered to a subject in need thereof. Neoangiogenesis is consequently inhibited. The subject may bear a vascularized tumor, may have polycystic kidney disease, may have diabetic retinopathy, may have rheumatoid arthritis, may have psoriasis, for example.

[09] Another aspect of the invention is a method of inhibiting tumor growth. An effective amount of an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 17, 19, 22, and 44, as shown in SEQ ID NO: 196, 200, 212, 230, 232, 238, and 271, respectively, is administered to a human subject bearing a tumor. The growth of the tumor is consequently inhibited.

[10] Still another aspect of the invention provides an isolated molecule comprising an antibody variable region which specifically binds to a TEM protein selected from the group consisting of: 3, 9, 17, 19, and 44, as shown in SEQ ID NO: 200, 212, 230, 232, and 271, respectively. The molecule can be, for example, an intact antibody molecule, a single chain variable region (ScFv), a monoclonal antibody, a humanized antibody, or a human antibody. The molecule can optionally be bound to a cytotoxic moiety, bound to a therapeutic moiety, bound to a detectable moiety, or bound to an anti-tumor agent.

[11] According to still another aspect of the invention an isolated and purified human transmembrane protein is provided. The protein is selected from the group consisting of: TEM 3, 9, 17, and 19 as shown in SEQ ID NO: 200, 212, 230, and 232, respectively.

- [12] Yet another aspect of the invention is an isolated and purified nucleic acid molecule comprising a coding sequence for a transmembrane TEM selected from the group consisting of: TEM 3, 9, 17, and 19 as shown in SEQ ID NO: 200, 212, 230, and 232, respectively. The isolated and purified nucleic acid molecule may optionally comprise a coding sequence selected from those shown in SEQ ID NO: 199, 211, 229, and 231.
- [13] Still another aspect of the invention is a recombinant host cell which comprises a nucleic acid molecule. The nucleic acid molecule comprises a coding sequence for a transmembrane TEM selected from the group consisting of: TEM 3, 9, 17, and 19 as shown in SEQ ID NO: 200, 212, 230, and 232, respectively. The recombinant host cell optionally comprises a coding sequence selected from those shown in SEQ ID NO: 199, 211, 229, and 231.
- [14] According to one embodiment of the invention a method is provided for inducing an immune response in a mammal. A nucleic acid molecule comprising a coding sequence for a human transmembrane protein selected from the group consisting of: TEM 1, 3, 9, 13, 17, 19, 22, 30, and 44 as shown in SEQ ID NO: , respectively, is administered to the mammal. An immune response to the human transmembrane protein is thereby induced in the mammal. Optionally the coding sequence is shown in SEQ ID NO: 196, 200, 212, 220, 230, 232, 238, 250 and 271.
- [15] According to yet another embodiment of the invention a method of inducing an immune response in a mammal is provided. A purified human transmembrane protein selected from the group consisting of: TEM 1, 3, 9, 13, 17, 19, 22, 30, and 44 as shown in SEQ ID NO: 196, 200, 212, 220, 230, 232, 238, 250 and 271, respectively, is administered to the mammal. An immune response to the human transmembrane protein is thereby induced in the mammal.

[16] Another aspect of the invention is a method for identification of a ligand involved in endothelial cell regulation. A test compound is contacted with an isolated and purified human transmembrane protein selected from the group consisting of 1, 3, 9, 13, 17, 30, 19, and 44 as shown in SEQ ID NO: 196, 200, 212, 220, 230, 232, 250, and 271. The isolated and purified human transmembrane protein is also contacted with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 13, 17, 30, 19, and 44 as shown in SEQ ID NO: 196, 200, 212, 220, 230, 232, 250, and 271 respectively. Binding of the molecule comprising an antibody variable region to the human transmembrane protein is determined. A test compound which diminishes the binding of the molecule comprising an antibody variable region to the human transmembrane protein is identified as a ligand involved in endothelial cell regulation.

[17] Yet another aspect of the invention is a method for identification of a ligand involved in endothelial cell regulation. A test compound is contacted with a cell comprising a human transmembrane protein selected from the group consisting of 1, 3, 9, 17, and 19 as shown in SEQ ID NO: 196, 200, 212, 230, and 232. The cell is also contacted with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 17, and 19 as shown in SEQ ID NO: 196, 200, 212, 230, and 232, respectively. Binding of the molecule comprising an antibody variable region to the cell is determined. A test compound which diminishes the binding of the molecule comprising an antibody variable region to the cell is identified as a ligand involved in endothelial cell regulation.

[18] Yet another aspect of the invention is a method for identification of a ligand involved in endothelial cell regulation. A test compound is contacted with a human transmembrane protein selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27,

28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275. Binding of a test compound to the human transmembrane protein is determined. A test compound which binds to the protein is identified as a ligand involved in endothelial cell regulation.

[19] Another embodiment of the present invention is a soluble form of a human transmembrane protein selected from the group consisting of: TEM 1, 3, 9, 17, 19, 22, 30, and 44 as shown in SEQ ID NO: 196, 200, 212, 230, 232, 238, 250, and 271 respectively. The soluble forms lack transmembrane domains. The soluble form may consist of an extracellular domain of the human transmembrane protein.

[20] Also provided by the present invention is a method of inhibiting neoangiogenesis in a patient. A soluble form of a human transmembrane protein is administered to the patient. Neoangiogenesis in the patient is consequently inhibited. The patient may bear a vascularized tumor, may have polycystic kidney disease, may have diabetic retinopathy, may have rheumatoid arthritis, or may have psoriasis, for example.

[21] Another embodiment of the invention provides a method of inhibiting neoangiogenesis in a patient. A soluble form of a human transmembrane protein is administered to the patient. Neoangiogenesis in the patient is consequently inhibited. The patient may bear a vascularized tumor, may have polycystic kidney disease, may have diabetic retinopathy, may have rheumatoid arthritis, or may have psoriasis, for example.

[22] According to still another aspect of the invention a method of identifying regions of neoangiogenesis in a patient is provided. A molecule comprising an antibody variable region which specifically binds to an

extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 13, 17, 19, 22, 30, and 44, as shown in SEQ ID NO: 196, 200, 212, 220, 230, 232, 238, 250, and 271, respectively, is administered to a patient. The molecule is bound to a detectable moiety. The detectable moiety is detected in the patient, thereby identifying neoangiogenesis.

[23] According to another aspect of the invention a method is provided for inducing an immune response to tumor endothelial cells in a patient. A mouse TEM protein selected from the group consisting of: 1, 2, 3, 9, 13, 17, 19, 22, and 30 as shown in SEQ ID NO: 291, 293, 299, 295, 303, 297, 301, 305, and 307, is administered to a patient in need thereof. An immune response to a human TEM protein is consequently induced.

[24] Still another embodiment of the invention is a method of screening for neoangiogenesis in a patient. A body fluid collected from the patient is contacted with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 17, 19, and 44, as shown in SEQ ID NO: 196, 200, 212, 230, 232, and 271, respectively. Detection of cross-reactive material in the body fluid with the molecule indicates neo-angiogenesis in the patient.

[25] Still another embodiment of the invention provides a method of inhibiting neoangiogenesis in a patient. A molecule comprising an antibody variable region which specifically binds to a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40 as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 and 224, 234, 242, 244, 252, 257, 259, 261, 263, and 265, is administered to the patient. Neoangiogenesis in the patient consequently inhibited.

[26] Yet another aspect of the invention is a method of screening for neoangiogenesis in a patient. A body fluid collected from the patient is

contacted with a molecule comprising an antibody variable region which specifically binds to a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 & 224, 234, 242, 244, 252, 257, 259, 261, 263, and 265, respectively. Detection of cross-reactive material in the body fluid with the molecule indicates neoangiogenesis in the patient.

[27] Also provided by the present invention is a method of promoting neoangiogenesis in a patient. A TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 & 224, 234, 242, 244, 252, 257, 259, 261, 263, and 265, is administered to a patient in need of neoangiogenesis. Neoangiogenesis in the patient is consequently stimulated.

[28] One embodiment of the invention provides a method of promoting neoangiogenesis in a patient. A nucleic acid molecule encoding a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: 201, 205, 207, 213, 217, 221 & 222, 233, 241, 243, 251, 256, 258, 260, 262, and 264, is administered to a patient in need of neoangiogenesis. The TEM protein is consequently expressed and neoangiogenesis in the patient is stimulated.

[29] Another embodiment of the invention provides a method of screening for neoangiogenesis in a patient. A TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 & 224, 234, 242, 244, 252, 257, 259, 261, 263, and 265, respectively, is detected in a body fluid collected from the patient. Detection of the TEM protein indicates neoangiogenesis in the patient.

[30] Another aspect of the invention is a method of screening for neoangiogenesis in a patient. A nucleic acid encoding a TEM protein

selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40 is detected in a body fluid collected from the patient. The nucleic acid is selected from the group consisting of those shown in SEQ ID NO: 201, 205, 207, 213, 217, 221 & 222, 233, 241, 243, 251, 256, 258, 260, 262, and 264. Detection of the TEM protein indicates neoangiogenesis in the patient.

[31] Yet another embodiment of the invention is an isolated and purified nucleic acid molecule which encodes a NEM protein selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289. The nucleic acid molecule optionally comprises a coding sequence as shown in SEQ ID NO: 278, 282, 284, and 288. The nucleic acid may be maintained in a recombinant host cell.

[32] The present invention also provides an isolated and purified NEM protein selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289.

[33] The present invention further provides an isolated molecule comprising an antibody variable region which specifically binds to a NEM protein selected from the group consisting of: 14, 22, 23, and 33, as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289.

[34] An additional embodiment of the present invention is a method of inhibiting neoangiogenesis. An effective amount of a NEM protein selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289 is administered to a subject in need thereof. Neoangiogenesis is thereby inhibited.

[35] A still further embodiment of the invention is a method to identify candidate drugs for treating tumors. Cells which express one or more TEM genes selected from the group consisting of: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11,

12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: : 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 221 & 222, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 256, 258, 260, 262, 266, 268, 270, 272, and 274, respectively, are contacted with a test compound. Expression of said one or more TEM genes is determined by hybridization of mRNA of said cells to a nucleic acid probe which is complementary to said mRNA. A test compound is identified as a candidate drug for treating tumors if it decreases expression of said one or more TEM genes. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs. Test compounds which increase expression can be identified as candidates for promoting wound healing.

[36] Yet another embodiment of the invention is a method to identify candidate drugs for treating tumors. Cells which express one or more TEM proteins selected from the group consisting of: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275, respectively, are contacted with a test compound. The amount of said one or more TEM proteins in said cells is determined. A test compound is identified as a candidate drug for treating tumors if it decreases the amount of one or more TEM proteins in said cells. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs. Alternatively, a test compound which increases the amount of one or more TEM proteins in said cells is identified as a candidate drug for treating wound healing.

[37] According to another aspect of the invention a method is provided to identify candidate drugs for treating tumors. Cells which express one or more TEM proteins selected from the group consisting of: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275, respectively, are contacted with a test compound. Activity of said one or more TEM proteins in said cells is determined. A test compound is identified as a candidate drug for treating tumors if it decreases the activity of one more TEM proteins in said cells. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs. Optionally the cells are endothelial cells. If a test compound increases the activity of one more TEM proteins in said cells it can be identified as a candidate drug for treating wound healing.

[38] An additional aspect of the invention is a method to identify candidate drugs for treating patients bearing tumors. A test compound is contacted with recombinant host cells which are transfected with an expression construct which encodes one or more TEM proteins selected from the group consisting of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275, respectively. Proliferation of said cells is determined. A test compound which inhibits proliferation of said cells is identified as a candidate drug for treating patients bearing tumors. A test compound which stimulates

proliferation of said cells is identified as a candidate drug for promoting neoangiogenesis, such as for use in wound healing.

[39] Another embodiment of the invention provides a method to identify candidate drugs for treating tumors. Cells which express one or more NEM genes selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 278, 282, 284, and 288, respectively, are contacted with a test compound. Expression of said one or more NEM genes is determined by hybridization of mRNA of said cells to a nucleic acid probe which is complementary to said mRNA. A test compound is identified as a candidate drug for treating tumors if it increases expression of said one or more NEM genes. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more NEMs.

[40] According to another aspect of the invention a method is provided to identify candidate drugs for treating tumors. Cells which express one or more NEM proteins selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, are contacted with a test compound. The amount of said one or more NEM proteins in said cells is determined. A test compound is identified as a candidate drug for treating tumors if it increases the amount of one more NEM proteins in said cells. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more NEMs.

[41] An additional aspect of the invention is a method to identify candidate drugs for treating tumors. Cells which express one or more NEM proteins selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, are contacted with a test compound. Activity of said one or more NEM proteins in said cells is determined. A test compound is identified as a candidate drug for treating

tumors if it increases the activity of said one or more NEM proteins in said cells. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more NEMs.

[42] Still another embodiment of the invention provides a method to identify candidate drugs for treating patients bearing tumors. A test compound is contacted with recombinant host cells which are transfected with an expression construct which encodes one or more NEM proteins selected from the group consisting of 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289. Proliferation of said cells is determined. A test compound which stimulates proliferation of said cells is identified as a candidate drug for treating patients bearing tumors.

[43] Another aspect of the invention is a method for identifying endothelial cells. One or more antibodies which bind specifically to a TEM or NEM protein selected from the group consisting of TEM : 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 30, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275 and NEM 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, is contacted with a population of cells. Cells in the population which have bound to said antibodies are detected. Cells which are bound to said antibodies are identified as endothelial cells. Optionally cells which have bound to said antibodies are isolated from cells which have not bound.

[44] Still another aspect of the invention is a method for identifying endothelial cells. One or more nucleic acid hybridization probes which are complementary to a TEM or NEM gene nucleic acid sequence selected from the group consisting of TEM : 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16,

17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 30, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275 and NEM 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, is contacted with nucleic acids of a population of cells. Nucleic acids which have specifically hybridized to said nucleic acid hybridization probes are detected. Cells whose nucleic acids specifically hybridized are identified as endothelial cells.

[45] Yet another embodiment of the invention is a method of inhibiting neoangiogenesis. An effective amount of an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a mouse TEM protein selected from the group consisting of: 1, 2, 3, 9, 17, and 19, as shown in SEQ ID NO: 291, 293, 299, 295, 297, and 301, respectively, is administered to a subject in need thereof. Neoangiogenesis is thereby inhibited. The subject may be a mouse, may bear a vascularized tumor, may have polycystic kidney disease, may have diabetic retinopathy, may have rheumatoid arthritis, or may have psoriasis, for example.

[46] These and other embodiments which will be apparent to those of skill in the art upon reading the specification provide the art with reagents and methods for detection, diagnosis, therapy, and drug screening pertaining to neoangiogenesis and pathological processes involving or requiring neoangiogenesis.

BRIEF DESCRIPTION OF THE DRAWINGS

[47] Fig. 1A-1B. vWF expression in colorectal cancers. vWF (red stain) was detected in vessels by in situ hybridization. At low power magnification (Fig. 1.A) vessels were often surrounded by a perivascular cuff of viable cells

(red arrows), with a ring of necrotic cells evident at the periphery (black arrows). At high power magnification (Fig. 1.B) the expression of vWF (red) was clearly localized to the vessels. Sections were counterstained with methyl green.

- [48] Fig. 2A-2D. Purification of Endothelial Cells (ECs) from human normal and malignant tissue. (Fig. 2A) Vessels (red) of frozen sections were stained by immunofluorescence with the P1H12 monoclonal antibody (Chemicon, Temecula, CA) and detected using a biotinylated goat anti-mouse IgG secondary antibody followed by rhodamine-linked streptavidin. The region stained is from within the lamina propria of normal colonic mucosa. Note that the larger vessels (arrowheads) and capillaries (arrows) are positive, and staining of hematopoietic cells was undetectable. E-cadherin positive epithelial cells (green) at the edge of the crypt were simultaneously visualized using a rabbit polyclonal antibody (Santa Cruz, Santa Cruz, CA), followed by a goat anti-rabbit IgG secondary antibody labelled with alexa (Molecular Probes, Eugene, OR). Sections were imaged at 60X magnification using confocal microscopy. (Fig. 2.B) To isolate pure populations from collagenase dispersed tissues, the epithelial and hematopoietic cell fractions were sequentially removed by negative selection with magnetic beads. The remaining cells were stained with P1H12 and ECs were isolated by positive selection with magnetic beads. (Fig. 2.C) RT-PCR analysis used to assess the purity of the EC preparations. Semiquantitative PCR analysis was performed on cDNA generated either directly from colorectal cancer tissue (unfractionated tumor) or from purified ECs isolated from normal colonic mucosa (normal EC fraction) or colorectal cancer (tumor EC fraction). PCR amplification of the epithelial specific marker cytokeratin 20 (CK20), demonstrated its expression was limited to the unfractionated tumor. Two endothelial specific markers, vWF and VE-cadherin (VE-Cad) showed robust amplification only in the endothelial fractions, validating the purity and enrichment protocol shown in (Fig. 2.B). The ubiquitous housekeeping enzyme GAPDH was observed in all samples.

No signal was detected in the no-template (NT) control. cDNA templates were diluted 1:10, 1:100, 1:1000, 1:4000, and 1:40,000 as indicated by the declining wedge. (Fig. 2.D) The relative expression level of select genes was determined by measuring the tag abundance from several SAGE libraries combined into four groups. The first was composed of ~193,000 tags from the two in vivo-derived EC preparations (Endothelial Cell Fraction) while the second contained a single library of ~57,000 tags containing macrophages and other leukocytes derived from the negative selection (Hematopoietic Fraction). The fourth library contained ~401,000 tags from cultured HUVEC and HMVEC (Endothelial Cells in Culture), and the fourth consisted of ~748,000 tags from 6 colon cancer cell lines in culture (Epithelial Cells). After normalization, the library with the highest tag number for each marker was given a value of 100%, and the corresponding relative expression levels of the remaining 3 libraries was plotted on the ordinate. Note the high level of CD31 present on hematopoietic cells, the likely cause of the impurity of the initial endothelial selection, compared with the selectivity of PIH12.

- [49] Fig. 3A- 3E). Expression of Pan-Endothelial Markers (PEMs) is limited to ECs. The endothelial origin of PEMs identified by SAGE was confirmed using a highly sensitive in situ hybridization assay. Localization of novel PEMs to the ECs was demonstrated by examining two representative PEMs, PEM3 (Fig. 3A) and PEM6 (Fig. 3B) in lung cancer and colon cancer, respectively. Hevin expression was readily detected in the ECs of a colon tumor (Fig. 3C) despite its low level of expression in cultured ECs. Expression of VEGFR2 was readily detectable in the ECs of both normal (Fig. 3D) and malignant colon tissue (Fig. 3E).
- [50] Fig. 4A-4J. Expression of Tumor Endothelial Markers (TEMs). (Fig. 4A) RT-PCR analysis confirmed the tumor specific expression of selected novel TEMs. Semiquantitative PCR analysis was performed on cDNA generated either from purified epithelial cells as a negative control (Control) or from purified ECs isolated from normal colonic mucosa (Normal ECs) or

colorectal cancer (Tumor ECs) from two different patients. Two endothelial specific markers, vWF and PEM6 showed robust amplification only in the endothelial fractions whereas the ubiquitous housekeeping enzyme GAPDH was observed in all samples. TEM1 (BSC-TEM1), TEM 17 (BSC-TEM7) and TEM22 (BSC-TEM9) were specifically expressed in tumor compared to normal ECs. The cDNA template was diluted 1:10, 1:100, 1:1000, and 1:10,000 as indicated by the declining wedge. (Fig. 4 B- 4J) The endothelial origin of TEMs identified by SAGE was confirmed using in situ hybridization as in Fig 3. Expression of TEM 1 (BSC-TEM1) (Fig. 4 B) and TEM17 (BSC-TEM7) (Fig. 4 C) was demonstrated to be highly specific to the ECs in colorectal cancers; sections were imaged in the absence of a counterstain to show the complete lack of detectable expression in the non-endothelial cells of the tumor. Expression of TEM17 (BSC-TEM7) in ECs was demonstrated in a metastatic liver lesion from a primary colorectal cancer (Fig. 4 D), a lung (Fig. 4 E), breast (Fig. 4 F), pancreatic (Fig. 4 G) and brain cancer (Fig. 4 H), as well as in a sarcoma (Fig. 4 I). TEM 17 (BSC-TEM7) was also localized to vessels during normal physiological angiogenesis of the corpus luteum (Fig. 4 J).

DETAILED DESCRIPTION OF THE INVENTION

[51] We identified 46 human genes that were expressed at significantly higher levels (> 10-fold) in tumor endothelium than in normal endothelium, and 33 genes that were expressed at significantly lower levels in human tumor versus normal endothelium. See Tables 2 and 4, respectively. Most of these genes were either not expressed or expressed at relatively low levels in Endothelial Cells (ECs) maintained in culture. Moreover, we identified 93 genes which are expressed in both normal and tumor human endothelium. Interestingly, the tumor endothelium genes were expressed in all tumors tested, regardless of its tissue or organ source. Most tumor endothelium genes were also expressed in corpus luteum and wounds.

[52] As the work has progressed, we have refined and classified our original 46 tumor endothelial markers. We have named these markers TEMs and renumbered them consecutively by the prevalence of their tags in our SAGE analysis. Originally we had not used a consecutive numbering system. Our non-consecutive numbering system has been renamed as BSC-TEMs. For most of the original 46 SAGE Tags, we now provide full-length nucleic acid and protein sequence. In some cases, the sequences were obtained through the public databases, in others the sequences were obtained by cloning and through the use of gene prediction tools. In some cases, we found SAGE Tags corresponding to genes having different splice variants or with known polymorphisms. For example, in one case the SAGE Tag BSC-TEM3 has been found to hybridize to an alternatively spliced form of the transcript encoding BSC-TEM7. The proteins encoded by the two transcripts are the same; therefore they are cumulatively called TEM7. A highly related sequence was found via homology searches, BSC-TEM7R. This paralog sequence is now called TEM3. See Table 2, which follows, showing tumor endothelial markers by order of prevalence (except for TEM 3). Column 1 indicates the prevalence number. Column 2 indicates the original nomenclature. Column 3 indicates the short tags. Column 4 indicates the long tags. Column 5 indicates the accession number in GenBank. Column 6 indicates the sequence identifiers for the short tag, the long tag, the full nucleic acid, and the protein. Column 7 provides a functional description, which is expanded below in the text.

TEM1	BSC- TEM1	GGGGCTGCC CA	GGGGCTGCCCAGCT GA	NM020404	SEQ ID NO : 94, 309, 195, 196	tumor endothelial marker 1 precursor
TEM2	BSC- TEM2	GATCTCCGT GT			SEQ ID NO: 95, 197, 198	sapiens tumor endothelial marker 2 (BSC-TEM2) mRNA/mouse Ras, dexamethasone-induced 1 (RASD1), mRNA
TEM3	BSC- TEM7 R				SEQ ID NO: 199, 200	human ortholog of mouse paralog of mouse TEM-7
TEM4		CTTCTTTGA G	CTTCTTTGAGTTT AA	AB034203	SEQ ID NO: 97, 311, 201, 202	Homo sapiens dickkopf-3 (DKK-3) mRNA,
TEM5	BSC- TEM4	TATTAAGTCT C	TATTAAGTCTCTTTG GA		SEQ ID NO: 98, 312, 203, 204	Tumor endothelial marker 4
TEM6		CAGGAGACC CC	CAGGAGACCCAGG CCC	X57766	SEQ ID NO: 99, 314, 205, 206	Human stromelysin-3 mRNA.
TEM7		GGAAATGTC AA	GGAAATGTCAGCAA GTA	BC002576	SEQ ID NO: 100, 315, 207, 208	matrix metalloproteinase 2 (gelatinase A, 72kD gelatinase, 72kD type IV collagenase)

TEM 8		CCTGGTTCA GT			SEQ ID NO:101, 316, 209, 210	HeyL transcription factor	
TEM 9	BSC- TEM5	TTTTTAAGAA C	TTTTTAAGAACTCGG GT		SEQ ID NO:102, 317, 211, 212		
TEM 10		TTTGGTTTTTC C	TTTGGTTTTCCAAAA GA	J03464, M18057, X02488	SEQ ID NO:103, 319, 213, 214	Human collagen alpha-2 type I mRNA, complete cds, clone pHCOL2A1.	
TEM 11		ATTTTGTATG A	ATTTTGTATGATTTT TA	NM_002508	SEQ ID NO:104, 321, 215, 216	nidogen/entactin	
TEM 12		ACTTTAGATG G	ACTTTAGATGGGAA GCC	X52022	SEQ ID NO:105, 322, 217, 218	H.sapiens RNA for type VI collagen alpha3 chain.	
TEM 13		GAGTGAGAC CC	GAGTGAGACCCAGG AGC	M11749	SEQ ID NO:106, 324, 219, 220	Human Thy-1 glycoprotein gene, complete cds.	
TEM 14		GTACACACA CC	GTACACACACCCCC ACC		SEQ ID NO:107, 325, 221, 223	Cystatin SN	

TEM 14	GTACACACA CC	GTACACACACCCCC ACC	X54667	SEQ ID NO:107, 325, 222, 224	H.sapiens mRNA for cystatin S.
TEM 15	CCACAGGGG AT	CCACAGGGGATTCT CCT	NM_000090	SEQ ID NO:108, 327, 225, 226	Human mRNA 3' region for pro-alpha1 (III) collagen.
TEM/BSC- 16/TEM6	TTAAAAGTCA C	TTAAAAGTCACTGTG CA		SEQ ID NO:109, 328, 227, 228	
TEM/BSC- 17/TEM7	ACAGACTGTT A	ACAGACTGTTAGCC AAG	AF279144	SEQ ID NO:110, 329, 229, 230	Human Tumor endothelial marker 7
TEM 18	CCACTGCAA CC			SEQ ID NO:111	
TEM/BSC- 19/TEM8	CTATAGGAG AC			SEQ ID NO:112, 330, 231, 232	
TEM 20	GTTCCACAG AA		NM_000089	SEQ ID NO:113, 233, 234	collagen, type I, alpha 2 (COL1A2)

TEM 21	TACCACCTC CC	TACCACCTCCCTTTC CT		SEQ ID NO:114, 331, 235, 236	Homo sapiens mRNA; cDNA DKFZp762B245 (from clone DKFZp762B245);
TEM 22	BSC- TEM9	GCCCTTTCTC T	NM_00603 9	SEQ ID NO:115, 334, 237, 238	endocytic receptor (macrophage mannose receptor family) (KIAA0709),
TEM 23		TTAAATAGCA C		SEQ ID NO:116, 335	no match
TEM 24		AGACATACT GA	NM_02264 8	SEQ ID NO:117, 336, 239, 240	Homo sapiens mRNA; cDNA DKFZp434G162 (from clone DKFZp434G162);
TEM 25		TCCCCCAGG AG	L35279, NM_00612 9	SEQ ID NO:118, 338, 241, 242	Homo sapiens (clone KT2) bone morphogenetic protein-1 (BMP-1) mRNA
TEM 26		AGCCCAAAG TG		SEQ ID NO:119	No Match
TEM 27		ACTACCATAA C	NM_00306 2	SEQ ID NO:120, 243, 244	Homo sapiens mRNA for MEGF5, partial cds.
TEM 28		TACAAATCGT T	NM_01485 9	SEQ ID NO:121, 339, 245, 246	Homo sapiens mRNA for KIAA0672 protein, complete cds.

TEM 29	TTGGGTGAA AA				SEQ ID NO:122, 247, 248	ESTs (2 unigene clusters)
TEM 30	CATTATCCAA A	CATTATCCAAAAACA AT	THC53402 9, X68742, AI262158, 250 AI88747, AI394565, AA679721		SEQ ID NO:123, 340, 249, 250	integrin, alpha 1
TEM 31	AGAAACCAC GG	AGAAACCACGGAAA TGG	NM_00184 5		SEQ ID NO:124, 341, 251, 252	hypothetical protein KIAA1164
TEM 32	ACCAAACC AC				SEQ ID NO:125	no match
TEM 33	TGAAATAAAC		NM_00025 5		SEQ ID NO:126, 253, 254	methylmalonyl Coenzyme A mutase
TEM 34	TTTGGTTTCC				SEQ ID NO:127	no match
TEM 35	GTGGAGACG GA	GTGGAGACGGACTC TGT	ESTAI188 535		SEQ ID NO:128, 345, 255, 358	est

TEM 36	TTTGTGTTGT A	TTTGTGTTGTATATT TA	NM_00437 0	SEQ ID NO:129, 346, 256, 257	est	
TEM 37	TTATGTTTAA T	TTATGTTTAAATAGTT GA	NM_00234 5	SEQ ID NO:130, 347, 258, 259	Human lumican mRNA, complete cds.	
TEM 38	TGGAAATGA C	TGGAAATGACCCAA AAA	NM_00008 8	SEQ ID NO:131, 348, 260, 261	collagen type1 alpha1	
TEM 39	TGCCACACA GT	TGCCACACAGTGAC TTG	NM_00323 9	SEQ ID NO:132, 350, 262, 263	Human transforming growth factor-beta 3 (TGF-beta3) mRNA, complete	
TEM 40	GATGAGGAG AC	GATGAGGAGACTGG CAA		SEQ ID NO:133, 351, 264, 265	collagen, type I, alpha 2	
TEM 41	ATCAAAGGTT T	ATCAAAGGTTTGATT TA		SEQ ID NO:134, 352, 266, 267	est	
TEM 42	AGTCACTAGT	AGTCACTAGTACAT AA	NM_02522 6	SEQ ID NO: 135, 353, 268, 269	ESTs	

TEM 43	TTCGGTTGG TC	TTCGGTTGGTCAAA GAT		SEQ ID NO:136, 354	No match
TEM 44	CCCCACACG GG	CCCCACACGGGCAA GCA	NM_01835 4v	SEQ ID NO: 137, 355, 270, 271	Homo sapiens cDNA FLJ11190 fis, clone PLACE1007583.
TEM 45	GGCTTGCCT TT	GGCTTGCCTTTTGT AT	NM_00036 6	SEQ ID NO:138, 356, 272, 273	est
TEM 46	ATCCCTTCCC G	ATCCCTTCCCGCCA CAC	NM_00268 8	SEQ ID NO:139, 357, 274, 275	Homo sapiens mRNA for peanut-like protein 1, PNU1L1 (hCDCrel-1).

[53] The studies described below provide the first definitive molecular characterization of ECs in an unbiased and general manner. They lead to several important conclusions that have direct bearing on long-standing hypotheses about angiogenesis. First, it is clear that normal and tumor endothelium are highly related, sharing many endothelial cell specific markers. Second, it is equally clear that the endothelium derived from tumors is qualitatively different from that derived from normal tissues of the same type and is also different from primary endothelial cultures. Third, these genes are characteristically expressed in tumors derived from several different tissue types, documenting that tumor endothelium, in general, is different from normal endothelium. Fourth, the genes expressed differentially in tumor endothelium are also expressed during other angiogenic processes such as corpus luteum formation and wound healing. It is therefore more appropriate to regard the formation of new vessels in tumors as "neoangiogenesis" rather than "tumor angiogenesis" *per se*. This distinction is important from a variety of perspectives, and is consistent with the idea that tumors recruit vasculature using much of, or basically the same signals elaborated during other physiologic or pathological processes. That tumors represent "unhealed wounds" is one of the oldest ideas in cancer biology.

[54] The nature and precise biological function of many of the Tumor Endothelial Markers (TEMs) identified here are unknown. Of the previously characterized genes shown in Table 2, it is intriguing that several encode proteins involved in extracellular matrix formation or remodelling (TEM 6, TEM 6, TEM 10, TEM 7, TEM 11, TEM 12, TEM 14, TEM 20, TEM 24, TEM 25, TEM 27, TEM 37, TEM 38, and TEM 40.) Deposition of extracellular matrix is likely critical to the growth of new vessels. Finally, it is perhaps not surprising that so many of the endothelial-specific transcripts identified here, whether expressed only in neovasculature or in endothelium in general, have not been previously characterized, and some are not even represented in EST databases. In part, this may be due to the fact that the EST databases are heavily biased toward certain

tissues, but moreover, may be due to the fact that even in highly vascularized tissues endothelial cells are still a relatively small proportion of the population. Thus, the sensitivity of the SAGE method is a particularly appropriate tool.

- [55] Sequence and literature study has permitted the following identifications to be made among the family of TEM proteins. TEM proteins have been identified which contain transmembrane regions. These include TEM 1, TEM 3, TEM 9, TEM 13, TEM 17, TEM 19, TEM 22, TEM 30, and TEM 44. TEM proteins have been identified which are secreted proteins, including TEM 4, TEM 6, TEM 7, TEM 10, TEM 12, TEM 14, TEM 20, TEM 25, TEM 27, TEM 31, TEM 36, TEM 37, TEM 38, and TEM 39. HeyL (TEM 8) is a transcription factor which may be involved in regulating TEMs as one or more groups. The protein corresponding to the tag for TEM44 was found in the public databases, but no biological function has yet been ascribed to it.
- [56] TEM 1 has been named endosialin in the literature. It has a signal sequence at amino acids 1-17 and a transmembrane domain at amino acids 686-708. Thus it is a cell surface protein. Its extracellular domain is at residues 1-685. Endosialin may be involved in endocytosis. The mouse ortholog is predicted to have a signal peptide at residues 1-21.
- [57] TEM 2 is a dexamethasone induced, ras related protein homolog of 266 amino acids. It has neither a signal sequence nor a transmembrane domain. Thus it is neither a cell surface nor a secreted protein. TEM 2 plays a role in signal transduction. It regulates alterations in cell morphology, proliferation, and cell-extracellular matrix interactions.
- [58] TEM 3 (originally termed TEM 7R) has both a signal sequence (at residues 1-24 or 1-30) and a transmembrane domain (at residues 456 - 477). Thus it is a cell surface protein. The portion of the protein which is extracellular is at amino acids 1- 455. TEM 3 has domains with homology to integrins, plexin,

and adhesion molecules. TEM 3 may regulate GTPases that control signal transduction pathways linking plasma membrane receptors to the actin cytoskeleton. In the mouse ortholog, the signal peptide is predicted to be residues 1-30.

[59] TEM 4 is also known as DKK -3. It has a signal sequence (residues 1-16), suggesting that it is a secreted protein. TEM 4 regulates *wnt* signaling, and it may be involved in vasculogenesis and *wnt*-dependent signaling for endothelial growth. TEM 4 is an inhibitor of Wnt oncogene and such inhibition can be determined by assay. Tsuji et al., *Biochem.Biophys.Res.Comm.* 268:20-4, 2000.

[60] TEM 5 appears to be neither secreted nor a cell surface protein. TEM 5 appears to be a component of a G protein - GTPase signaling pathway.

[61] TEM 6 is also known as stromelysin - 3 /Matrix metalloproteinase 11 (MMP -11). It has a signal sequence at residues 1-31, but no transmembrane domain. It has an alternative signal peptide splice site at residues 108-109. Thus it appears to be a secreted protein. TEM 6 belongs to the zinc metaloprotease family, also known as the *matrixin* subfamily. TEM 6 is expressed in most invasive carcinomas. Alpha 1 - protease inhibitor is a natural substrate of MMP 11. TEM 6 degrades extracellular matrix proteins such as collagen and is involved in extracellular matrix remodeling and cell migration. Stromelysin can be assayed using a casein-resorufin substrate, for example. See Tortorella and Arner, *Inflammation Research* 46 Supp. 2:S122-3, 1997.

[62] TEM 7 is a protein of many names, also being known as matrix metalloproteinase 2, gelatinase A, and 72KD type IV collagenase. TEM 7 has a signal sequence at residues 1-26 and is a secreted protein. Like TEM 6, TEM 7 belongs to the *matrixin* subfamily (zinc metalloproteinases). TEM 7 cleaves gelatin type I, collagen type I, IV, V, VII and X. TEM 7 associates with integrin on the surface of endothelial cells and promotes vascular invasion. TEM 7 is

involved in tissue remodeling. TEM 7 can be assayed using zymography or quenched fluorescent substrate hydrolysis, for example. Garbett, et al., *Molecular Pathology* 53:99-106, 2000. A fluorogenic matrix metalloproteinase substrate assay can also be used which employs methoxycoumarin containing septapeptide analog of the alpha2(I) collagen cleavage site. See Bhide et al., *J. Periodontology* 71:690-700, 2000.

[63] TEM 8 is HEYL protein. It has neither a signal sequence nor a transmembrane domain. It is related to the hairy/Enhancer of split genes. TEM 8 is likely a nuclear protein, having a role as a transcription factor. TEM 8 belongs to a new class of Notch signal transducers and plays a key role in various developmental processes, such as vascular development, somatogenesis and neurogenesis. SNP's at residues 615 and 2201 have Cytosine bases. Notch 3 mutations underlie the CADASIL vascular disorder. See *Mech Dev* 2000 Nov; 98 (1-2):175

[64] TEM 9 is a G- protein coupled receptor homolog, having both a signal sequence at residues 1-26 and 7 transmembrane domains. Thus it is a cell surface protein. Its extracellular region resides in amino acids 1-769. Its transmembrane domains are at residues 817-829 (TM2 and TM3), residues 899-929 (TM4 and TM5), and residues 1034-1040 (TM6 and TM7). TEM 9 acts as a G-protein coupled receptor with extracellular domains characteristic of cell adhesion proteins. One of its splice variants may function as a soluble receptor. TEM 9 may regulate cell polarity and cell migration. It may be involved in exocytosis based on latrophilin function. The mouse ortholog has a predicted signal peptide at residues 1-29.

[65] TEM 10 is collagen type I, alpha2 (COL1A2), which has a signal sequence at residues 1-22. It is an extracellular matrix (ECM) protein which is secreted subsequent to synthesis. TEM 10 interacts with a number of proteins including other ECM proteins, certain growth factors, and matrix metalloproteases. TEM

10 is required for the induction of endothelial tube formation and is involved in tissue remodeling. A variant at nucleotide 3233 which substitutes an A, is associated with osteogenesis imperfecta type IV. A variant at nucleotide 4321 substituting an A retains a wild type phenotype. Nucleotide 715 is a site of a polymorphism. Nucleotides 695-748 are deleted in Ehlers-Danos syndrome. Other mutations are associated with idiopathic osteoporosis, and atypical Marfan syndrome. Variants are known at nucleotides 226(T,C), 314(A,C), 385(T,C), 868(G,A), 907(C,T), 965(A,G), 970(T,A), 1784 (G,C), 2017(T,G), 2172(C,A), 2284(T,C), 2308(T,C), 2323(T,G), 2344(T,G), 2604(G,A), 2974(A,T), 2903(A,G), 2995(C,T), 3274(C,T), 3581(A,C), 3991(A,C), 4201(G,T), 4434(C,T), 4551(A,C), 4606(C,A), 4947(T,C), 4978(C,T), 4982(G,T), 5051(G,T). PolyA sites are located at nucleotides 4450, 4550, 4885, and 5082. PolyA signals are located at 4420-4424, 4515-4520, 4529-4534, 4866-4871, 5032-5037, 5053-5058. TEM 10, 20, and 40 derive from the same gene but are different isoforms having different lengths.

[66] TEM 11 is Nidogen /Entactin. It is a secreted protein which has a signal sequence at residues 1-28. TEM 11 is an extracellular matrix protein which is a component of a basement membrane. TEM 11 binds to laminin and collagen IV and other extracellular matrix proteins. TEM 11 regulates capillary formation and is involved in tissue remodelling. Variations have been observed at nucleotides 4265(T,C), 4267(G,C,T), and 4738(T,G). Nidogen can be assayed by its effect on the morphology of astrocytes. See Grimpe et al., GLIA 28:138-49, 1999.

[67] TEM 12 is the alpha 3 chain of collagen type VI. It has a signal sequence at residues 1-25. A secreted protein, TEM 12 is an extracellular matrix protein. TEM 12 has a splice variant. TEM 12 is a major constituent of vascular subendothelium and is involved in tissue remodeling. It regulates platelet activation and aggregation. Alternatively spliced domains are located at nucleotides 347-964, 965-1567, 2153-3752, and 4541-5041.

- [68] TEM 13 is also known as Thy -1 glycoprotein. It has both a signal sequence (at residues 1-19) and a transmembrane domain (at residues 143-159). Residues 131-161 are removed in a matured form of the protein. The extracellular region of the protein is residues 1- 142 or residues 1-130. TEM 13 has a glycosyl phosphatidylinositol (GPI) anchor at residue 130 anchoring it to the membrane. TEM 13 is detectable in its soluble form in human serum. TEM 13 is reported to be a marker for activated endothelial cells (a marker of adult but not embryonic angiogenesis). TEM 13 on vascular endothelial cells may function as a possible vascular permeability modulator. Antibody to Thy-1 is a mitogenic signal for the CD4+CD45+ and CD8+CD45+ cells, but fails to induce proliferation in the CD45- T cells. Pingel et al., *International Immunology* 6:169-78, 1994. Thy-1 can be assayed as an inhibitor of such signal.
- [69] TEM 14 is also known as cystatin S. It is a secreted protein with a signal sequence at residues 1-20 and an extracellular region at residues 1-141. It is a cysteine protease inhibitor. TEM 14 may regulate cysteine protease function involved in angiogenesis and tissue remodeling. TEM14 is an inhibitor of the activity of papain and such inhibition can be assayed. Hiltke et al., *J. Dental Research* 78:1401-9, 1999.
- [70] TEM 15 is collagen type III, alpha 1 (COL3A1). It has a signal sequence (residues 1-23) and is secreted. Type III collagen binds to von Willebrand factor. It is involved in cell-cell adhesion, proliferation, and migration activities. Variants at nucleotides 2104(C,A), 2194(G,A), 2346(C,T), 2740(C,T), 3157(T), 3468(G), 3652(T), 3666(C), 3693(C), 3755(G), 3756(T), 3824(C), 4546(A, G), 4661(G), 4591(C,T), 4665(C), 5292(C), 5293(C), and 5451 (A) have been observed.
- [71] TEM 16 is a tensin homolog which is apparently an intracellular protein. It may have splice variants or isoforms. One form with 1704 amino acids has a region at the N-terminal domain which is similar to a tumor suppressor protein,

phosphatase and tensin homolog (PTEN). Tensin is a focal adhesion molecule that binds to actins and phosphorylated proteins. It is involved in cell migration linking signal transduction pathways to the cytoskeleton. PTEN regulates tumor induced angiogenesis.

[72] TEM 17 (BSC-TEM 7) has a signal sequence which includes residues 1-18 and a transmembrane domain at residues 427-445. It is a cell surface marker with an extracellular region comprising residues 1-426. It has homologs in both mouse and *C. elegans*. Residues 137-244 share weak homology with nidogen; residues 280-344 share homology to PSI domains found in plexin, semaphorins and integrin beta subunits. Variants have been observed at nucleotides 1893(A,G), 1950(C,G), 2042(A,G), and 2220(G,A). In mouse TEM 17 the signal sequence includes residues 1-19.

[73] TEM 19 was originally reported to be tumor endothelial marker 8, *i.e.*, BSC-TEM 8. It has a signal sequence at residues 1-27 and a transmembrane domain at residues 322-343. It is a cell surface protein having an extracellular region at residues 1-321. TEM 19 has a von Willebrand Factor (vWF) A domain at residues 44-216; a domain at residues 34-253 which is found in leukointegrin alpha D chain; and a domain at residues 408-560 found in PRAM-1 or adaptor molecule -1 of the vinculin family. TEM 19's function is adhesion related. vonWillebrand Factor domains are typically involved in a variety of functions including vascular processes. TEM 19 may play a role in the migration of vascular endothelial cells. The mouse ortholog has a predicted signal peptide at residues 1-27.

[74] TEM 20 is collagen type I, alpha 2 (COL1A2). It has a signal sequence at residues 1-22 and is a secreted extracellular matrix protein. TEM 20 induces endothelial tube formation *in vitro* and is involved in tissue remodeling. Variants have been observed at nucleotides 226(T,C), 314(A,C), 385(T,C), 868 (G,A), 907(C,T), 965(A,G), 970(T,A), 1784(G,C), 2017(T,G), 2172(C,A), 2284(T,C),

2308(T,C), 2323(T,G), 2344(T,G), 2604(G,A), 2794(A,T), 2903(A,G),
 2995(C,T), 3274(C,T), 3581(A,C), 3991(A,C), 4201(G,T), 4434(C,T), 4551(A,C),
 4606(C,A), 4895-4901(-, GGACAAC), 4947(T,C), 4978(C,T), 4982(G,T),
 5051(G,T).

[75] TEM 21 is a Formin – like protein homolog which is an intracellular protein. Formin related proteins interact with Rho family small GTPases, profilin, and other actin associated proteins. Formin-binding proteins bind to FH1 domains with their WW domains. TEM 21 has a proline rich FH1 domain at residues 221-449. Formin related proteins play crucial roles in morphogenesis, cell polarity, cytokinesis and reorganization of the actin cytoskeleton. They may also regulate apoptosis, cell adhesion and migration.

[76] TEM 22 is an endocytic receptor in the macrophage mannose receptor family. It has both a signal sequence at residues 1-30 and a transmembrane domain at residues 1415-1435, and resides on the cell surface. Its extracellular domain is amino acids 1- 1414. TEM 22 may be present as a soluble (secreted) form and act as an inhibitor. It may bind secreted phospholipase A2 (sPLA2) and mediate biological responses elicited by sPLA2. TEM 22 may have endocytic properties for sPLA2 and mediate endocytosis for endothelial related proteins. It may promote cell adhesion and be involved in cell-cell communication. Variations have been observed at nucleotide 5389 (A, G). TEM 22 mediates uptake of micro-organisms and host-derived glycoproteins. Groger et al., J. Immunology 165:5428-34, 2000.

[77] TEM 24 is tensin, an intracellular protein. It is a focal adhesion molecule that binds to actin filaments and interacts with phosphotyrosine containing proteins. It may mediate kinase signaling activities and regulate cellular transformation. Variations have been observed at nucleotides 2502 (A, G), 2622(A, G), 6027(A, G). TEM24 binds to actin filaments and interacts with phosphotyrosine-containing proteins. Chen et al., Biochem. J. 351 Pt2:403-11,

2000. TEM24 also binds to phosphoinositide3-kinase. Auger et al., J. Bio. Chem. 271:23452-7, 1996 TEM 24 also binds to nuclear protein p130. Lo et al., Bioessays 16:817-23, 1994.

[78] TEM 25 is Bone morphogenic protein 1 (BMP-1) which has a signal sequence at residues 1-22. It is a secreted protein. There are at least 6 isoforms of BMP-1 as well as splice variants which add carboxy terminal CUB domains and an additional EGF domain. TEM 25 is a metalloprotease enzyme. It cleaves the C-terminal propeptide of collagen type I, II and III and laminin 5 gamma 2 , proteins that are important for vascular processes. It is involved in cartilage formation. Variations have been observed at nucleotides 3106(C,T), 3248(G,A), 3369(G,A). TEM 25 cleave probiglycan at a single site, removing the propeptide and producing a biglycan molecule with an NH(2) terminus identical to that of the mature form found in tissues. Scft et al., J. Biol. Chem. 275:30504-11, 2000. Laminin alpha 3 and gamma2 short chains are substraates of TEM 25. Amano et al., J. Biol. Chem. 275:22728-35, 2000.

[79] TEM 27 is known as Slit homolog 3, a secreted protein with a signal sequence at residues 1-27. TEM 27 is a secreted guide protein involved in migration, repulsion and patterning. It interacts with "round about" receptors (Robo receptors). TEM 27 may interact with extracellular matrix (ECM) proteins and is involved in cell adhesion. Variations have been observed at nucleotides 4772 (C,T)

[80] TEM 28 is similar to mouse nadrin (neuron specific GTPase activating protein). TEM 28 is an intracellular protein with a RhoGAP domain. The RhoGAP domain activates RhoA, Rac1, and Cdc42 GTPases. It is involved in the reorganization of actin filaments and enhancing exocytosis. It may also be involved in cell signalling. Variations have been observed at nucleotide 3969 (A,C),

- [81] TEM 29 is protein tyrosine phosphatase type IVA, member 3, isoform 1, an intracellular protein. It has alternate splice variants. TEM 29 belongs to a small class of prenylated protein tyrosine phosphatases (PTPs). It may be membrane associated by prenylation. PTPs are cell signaling molecules and play regulatory roles in a variety of cellular processes and promote cell proliferation. PTP PRL-3 regulates angiotensin -II induced signaling events.
- [82] TEM 30 is integrin alpha 1, a cell surface protein having both a signal sequence (residues 1-28) and a transmembrane domain (residues 1142-1164). Its extracellular region includes amino acids 1-1141. TEM 30 is a receptor for laminin and collagen. It mediates a variety of adhesive interactions. TEM 30 is abundantly expressed on microvascular endothelial cells. It stimulates endothelial cell proliferation and vascularization. TEM 30 may regulate angiostatin production. Variations have been observed at nucleotide 418 (C,T). TEM 30 activates the Ras/Raf/mitogen-activated protein kinase pathway promoting fibroblast cell proliferation. It also acts to inhibit collagen and metalloproteinase synthesis. Pozzi et al., Proc. Nat. Acad. Sci. USA 97:2202-7, 2000,
- [83] TEM 31 is Collagen IV alpha 1 (COL4A1) a secreted protein with a at residues 1-27. TEM 31 is a component of the basement membrane. It binds to alpha3 beta 1 integrin and promotes integrin mediated cell adhesion. Non-collagenous domains of type IV subunits are involved in tumoral angiogenesis. TEM 31 is involved in tissue remodeling. Variations have been observed at nucleotide 4470 (C,T)
- [84] TEM 33 is methylmalonyl Co-A Mutase a protein which is localized in the mitochondrial matrix. It degrades several amino acids, odd-numbered-acid fatty acids, and cholesterol to the tricarboylic acid cycle. A defect in TEM 33 causes a fatal disorder in organic acid metabolism termed methylmalonic aciduria. Variations have been observed at nucleotides 1531(G,A), 1671(G,A), 2028(T,C), 2087(G,A), 2359(A,G), 2437(C,A), 2643(G,C), 2702(G,C). TEM 33

converts L-methylmalonyl CoA to succinyl CoA. This reaction can be assayed as is known in the art. See, e.g., Clin. Chem. 41(8 Pt I):1164-70, 1995.

- [85] TEM 36 is collagen type XII, alpha1 (COL12A1), an extracellular matrix protein having a signal sequence at residues 1-23 or 24. TEM 36 has von Willebrand Factor (vWF) type A domains, Fibronectin type III domains, and thrombospondin N-terminal like domain. TEM 36 is expressed in response to stress environment. TEM 36 may organize extracellular matrix architecture and be involved in matrix remodeling. There are two isoforms of the protein, a long form and a short form. The short form is missing amino acids 25-1188, and therefore nucleotides 73 to 3564. Both forms share the signal sequence and are therefore both secreted.
- [86] TEM 37 is lumican, an extracellular matrix sulfated proteoglycan having a signal sequence at residues 1-18. Lumican interacts with proteins that are involved in matrix assembly such as collagen type I and type VI; it is involved in cell proliferation and tissue morphogenesis. Lumican plays an important role in the regulation of collagen fiber assembly. Variations have been observed at nucleotides 1021(G,T), 1035(A,G), 1209(A,G), 1259(A,C), 1418(C,A), 1519(T,A). TEM 37 is a binding partner of TGF- β . See FASEB J. 15:559-61, 2000. One assay that can be used to determine TEM 37 activity is a collagen fibril formation/sedimentation assay. Svensson et al., FEBS Letters 470:178-82, 2000.
- [87] TEM 38 is collagen type I, alpha 1 (COL1A1), an extracellular matrix protein having a signal sequence at residues 1-22. Type I collagen promotes endothelial cell migration and vascularization and induces tube formation and is involved in tissue remodelling. Telopeptide derivative is used as a marker for malignancy and invasion for certain cancer types. Variations have been observed at nucleotides 296(T,G), 1810(G,A), 1890(G,A), 2204(T,A), 3175(G,C), 3578(C,T), 4298(C,T), 4394(A,T), 4410(A,C), 4415(C,A), 4419 (A,T), 4528(C,A), 4572(G,T), 4602(T,C), 5529(T,C), 5670(C,T), 5985(C,T), 6012(C,T).

- [88] TEM 39 is transforming growth factor β -3 (TGF-beta3). It has a signal sequence at residues 1-23. It is a secreted protein. TEM 39 regulates cell growth and differentiation. TGF-beta isoforms play a major role in vascular repair processes and remodeling. Variations have been observed at nucleotide 2020(G,T).
- [89] TEM 41 is similar to Olfactomedin like protein. It appears to be an intracellular protein, having no obvious predicted signal sequence. Olfactomedin is the major glycoprotein of the extracellular mucous matrix of olfactory neuroepithelium. TEM 41 shares homology with latrophilin (extracellular regions) which has cell-adhesive type domains. TEM 41 may be involved in adhesive function.
- [90] TEM 42 is MSTP032 protein, a cell surface protein having a transmembrane domain at residues 42-61. Its function is unknown and it shares little homology with other proteins. Variations have been observed at nucleotides 418(A,T), 724(C,A).
- [91] TEM 44 is a hypothetical protein FLJ11190 (NM_018354) which has two predicted transmembrane domains at residues 121-143 and 176-197. Residues 144-175 may form an extracellular region. TEM 44's function is not known and shares no homology to other known proteins.
- [92] TEM 45 is tropomyosin 1 (alpha), a protein which is intracellular. It forms dimers with a beta subunit. It influences actin function. TEM 45 may be involved in endothelial cell cytoskeletal rearrangement. Variations have been observed at nucleotides 509(A,C), 621(A,C), 635(T,G), 642(C,G), 1059(G,T).
- [93] TEM 46 is peanut-like 1 protein/septin 5, which belongs to the septin family. Proteins in the septin family bind to GTP and phosphatidylinositol 4,5-bisphosphate. They are involved in the signal transduction cascades controlling cytokinesis and cell division.

- [94] NEM 4 is a member of the small inducible cytokine subfamily A (cys-cys), member 14 (SCYA14). NEM4 is a secreted protein characterized by two adjacent cysteine residues. One isoform lacks internal 16 amino acids compared to isoform 2.
- [95] NEM 22 shares homology with guanylate kinase-interacting protein 1Maguin-1. It is a membrane associated protein.
- [96] NEM 23 is human signaling lymphocytic activation molecule (SLAM). It has a signal sequence at residues 1-20. The extracellular domain may reside at residues 21-237. There is a secreted isoform of the protein.
- [97] NEM33 is netrin 4. It induces neurite outgrowth and promotes vascular development. At higher concentration, neurite outgrowth is inhibited.
- [98] ECs represent only a minor fraction of the total cells within normal or tumor tissues, and only those EC transcripts expressed at the highest levels would be expected to be represented in libraries constructed from unfractionated tissues. The genes described in the current study should therefore provide a valuable resource for basic and clinical studies of human angiogenesis in the future. Genes which have been identified as tumor endothelial markers (TEMs) correspond to tags shown in SEQ ID NOS: 94-139, 173-176, 180-186. Genes which have been identified as normal endothelial markers (NEMs) correspond to tags shown in SEQ ID NOS: 140-172. Genes which have been identified as pan-endothelial markers (PEMs) *i.e.*, expressed in both tumor and normal endothelial cells correspond to tags shown in SEQ ID NOS: 1-93. Genes which have been previously identified as being expressed predominantly in the endothelium correspond to PEM tags shown in SEQ ID NOS: 1-6, 8, 10-15. Markers in each class can be used interchangeably for some purposes.

[99] Isolated and purified nucleic acids, according to the present invention are those which are not linked to those genes to which they are linked in the human genome. Moreover, they are not present in a mixture such as a library containing a multitude of distinct sequences from distinct genes. They may be, however, linked to other genes such as vector sequences or sequences of other genes to which they are not naturally adjacent. Tags disclosed herein, because of the way that they were made, represent sequences which are 3' of the 3' most restriction enzyme recognition site for the tagging enzyme used to generate the SAGE tags. In this case, the tags are 3' of the most 3' most NlaIII site in the cDNA molecules corresponding to mRNA. Nucleic acids corresponding to tags may be RNA, cDNA, or genomic DNA, for example. Such corresponding nucleic acids can be determined by comparison to sequence databases to determine sequence identities. Sequence comparisons can be done using any available technique, such as BLAST, available from the National Library of Medicine, National Center for Biotechnology Information. Tags can also be used as hybridization probes to libraries of genomic or cDNA to identify the genes from which they derive. Thus, using sequence comparisons or cloning, or combinations of these methods, one skilled in the art can obtain full-length nucleic acid sequences. Genes corresponding to tags will contain the sequence of the tag at the 3' end of the coding sequence or of the 3' untranslated region (UTR), 3' of the 3' most recognition site in the cDNA for the restriction endonuclease which was used to make the tags. The nucleic acids may represent either the sense or the anti-sense strand. Nucleic acids and proteins although disclosed herein with sequence particularity, may be derived from a single individual. Allelic variants which occur in the population of humans are including within the scope of such nucleic acids and proteins. Those of skill in the art are well able to identify allelic variants as being the same gene or protein. Given a nucleic acid, one of ordinary skill in the art can readily determine an open reading frame present, and consequently the sequence of a polypeptide encoded by the open reading frame and, using techniques well known in the art, express such protein in a suitable

host. Proteins comprising such polypeptides can be the naturally occurring proteins, fusion proteins comprising exogenous sequences from other genes from humans or other species, epitope tagged polypeptides, etc. Isolated and purified proteins are not in a cell, and are separated from the normal cellular constituents, such as nucleic acids, lipids, etc. Typically the protein is purified to such an extent that it comprises the predominant species of protein in the composition, such as greater than 50, 60 70, 80, 90, or even 95% of the proteins present.

[100] Using the proteins according to the invention, one of ordinary skill in the art can readily generate antibodies which specifically bind to the proteins. Such antibodies can be monoclonal or polyclonal. They can be chimeric, humanized, or totally human. Any functional fragment or derivative of an antibody can be used including Fab, Fab', Fab2, Fab'2, and single chain variable regions. So long as the fragment or derivative retains specificity of binding for the endothelial marker protein it can be used. Antibodies can be tested for specificity of binding by comparing binding to appropriate antigen to binding to irrelevant antigen or antigen mixture under a given set of conditions. If the antibody binds to the appropriate antigen at least 2, 5, 7, and preferably 10 times more than to irrelevant antigen or antigen mixture then it is considered to be specific.

[101] Techniques for making such partially to fully human antibodies are known in the art and any such techniques can be used. According to one particularly preferred embodiment, fully human antibody sequences are made in a transgenic mouse which has been engineered to express human heavy and light chain antibody genes. Multiple strains of such transgenic mice have been made which can produce different classes of antibodies. B cells from transgenic mice which are producing a desirable antibody can be fused to make hybridoma cell lines for continuous production of the desired antibody. See for example, Nina D. Russel, Jose R. F. Corvalan, Michael L. Gallo, C. Geoffrey Davis, Liise-Anne Pirofski. Production of Protective Human Antipneumococcal Antibodies by Transgenic Mice with Human Immunoglobulin Loci *Infection and Immunity* April 2000, p.

1820-1826; Michael L. Gallo, Vladimir E. Ivanov, Aya Jakobovits, and C. Geoffrey Davis. The human immunoglobulin loci introduced into mice: V (D) and J gene segment usage similar to that of adult humans *European Journal of Immunology* 30: 534-540, 2000; Larry L. Green. Antibody engineering via genetic engineering of the mouse: XenoMouse strains are a vehicle for the facile generation of therapeutic human monoclonal antibodies *Journal of Immunological Methods* 231 11-23, 1999; Yang X-D, Corvalan JRF, Wang P, Roy CM-N and Davis CG. Fully Human Anti-interleukin-8 Monoclonal Antibodies: Potential Therapeutics for the Treatment of Inflammatory Disease States. *Journal of Leukocyte Biology* Vol. 66, pp401-410 (1999); Yang X-D, Jia X-C, Corvalan JRF, Wang P, CG Davis and Jakobovits A. Eradication of Established Tumors by a Fully Human Monoclonal Antibody to the Epidermal Growth Factor Receptor without Concomitant Chemotherapy. *Cancer Research* Vol. 59, Number 6, pp1236-1243 (1999) ; Jakobovits A. Production and selection of antigen-specific fully human monoclonal antibodies from mice engineered with human Ig loci. *Advanced Drug Delivery Reviews* Vol. 31, pp: 33-42 (1998); Green L and Jakobovits A. Regulation of B cell development by variable gene complexity in mice reconstituted with human immunoglobulin yeast artificial chromosomes. *J. Exp. Med.* Vol. 188, Number 3, pp: 483-495 (1998); Jakobovits A. The long-awaited magic bullets: therapeutic human monoclonal antibodies from transgenic mice. *Exp. Opin. Invest. Drugs* Vol. 7(4), pp : 607-614 (1998) ; Tsuda H, Maynard-Currie K, Reid L, Yoshida T, Edamura K, Maeda N, Smithies O, Jakobovits A. Inactivation of Mouse HPRT locus by a 203-bp retrotransposon insertion and a 55-kb gene-targeted deletion: establishment of new HPRT-Deficient mouse embryonic stem cell lines. *Genomics* Vol. 42, pp: 413-421 (1997) ; Sherman-Gold, R. Monoclonal Antibodies: The Evolution from '80s Magic Bullets To Mature, Mainstream Applications as Clinical Therapeutics. *Genetic Engineering News* Vol. 17, Number 14 (August 1997); Mendez M, Green L, Corvalan J, Jia X-C, Maynard-Currie C, Yang X-d, Gallo M, Louie D, Lee D, Erickson K, Luna J, Roy C, Abderrahim H, Kirschenbaum F, Noguchi M,

Smith D, Fukushima A, Hales J, Finer M, Davis C, Zsebo K, Jakobovits A. Functional transplant of megabase human immunoglobulin loci recapitulates human antibody response in mice. *Nature Genetics* Vol. 15, pp: 146-156 (1997); Jakobovits A. Mice engineered with human immunoglobulin YACs: A new technology for production of fully human antibodies for autoimmunity therapy. *Weir's Handbook of Experimental Immunology, The Integrated Immune System* Vol. IV, pp: 194.1-194.7 (1996) ; Jakobovits A. Production of fully human antibodies by transgenic mice. *Current Opinion in Biotechnology* Vol. 6, No. 5, pp: 561-566 (1995) ; Mendez M, Abderrahim H, Noguchi M, David N, Hardy M, Green L, Tsuda H, Yoast S, Maynard-Currie C, Garza D, Gemmill R, Jakobovits A, Klapholz S. Analysis of the structural integrity of YACs comprising human immunoglobulin genes in yeast and in embryonic stem cells. *Genomics* Vol. 26, pp: 294-307 (1995); Jakobovits A. YAC Vectors: Humanizing the mouse genome. *Current Biology* Vol. 4, No. 8, pp: 761-763 (1994); Arbones M, Ord D, Ley K, Ratech H, Maynard-Curry K, Otten G, Capon D, Tedder T. Lymphocyte homing and leukocyte rolling and migration are impaired in L-selectin-deficient mice. *Immunity* Vol. 1, No. 4, pp: 247-260 (1994); Green L, Hardy M, Maynard-Curry K, Tsuda H, Louie D, Mendez M, Abderrahim H, Noguchi M, Smith D, Zeng Y, et. al. Antigen-specific human monoclonal antibodies from mice engineered with human Ig heavy and light chain YACs. *Nature Genetics* Vol. 7, No. 1, pp: 13-21 (1994); Jakobovits A, Moore A, Green L, Vergara G, Maynard-Curry K, Austin H, Klapholz S. Germ-line transmission and expression of a human-derived yeast artificial chromosome. *Nature* Vol. 362, No. 6417, pp: 255-258 (1993) ; Jakobovits A, Vergara G, Kennedy J, Hales J, McGuinness R, Casentini-Borocz D, Brenner D, Otten G. Analysis of homozygous mutant chimeric mice: deletion of the immunoglobulin heavy-chain joining region blocks B-cell development and antibody production. *Proceedings of the National Academy of Sciences USA* Vol. 90, No. 6, pp: 2551-2555 (1993); Kucherlapati et al.; U.S. 6,1075,181.

[102] Antibodies can also be made using phage display techniques. Such techniques can be used to isolate an initial antibody or to generate variants with altered specificity or avidity characteristics. Single chain Fv can also be used as is convenient. They can be made from vaccinated transgenic mice, if desired. Antibodies can be produced in cell culture, in phage, or in various animals, including but not limited to cows, rabbits, goats, mice, rats, hamsters, guinea pigs, sheep, dogs, cats, monkeys, chimpanzees, apes.

[103] Antibodies can be labeled with a detectable moiety such as a radioactive atom, a chromophore, a fluorophore, or the like. Such labeled antibodies can be used for diagnostic techniques, either *in vivo*, or in an isolated test sample. Antibodies can also be conjugated, for example, to a pharmaceutical agent, such as chemotherapeutic drug or a toxin. They can be linked to a cytokine, to a ligand, to another antibody. Suitable agents for coupling to antibodies to achieve an anti-tumor effect include cytokines, such as interleukin 2 (IL-2) and Tumor Necrosis Factor (TNF); photosensitizers, for use in photodynamic therapy, including aluminum (III) phthalocyanine tetrasulfonate, hematoporphyrin, and phthalocyanine; radionuclides, such as iodine-131 (^{131}I), yttrium-90 (^{90}Y), bismuth-212 (^{212}Bi), bismuth-213 (^{213}Bi), technetium-99m ($^{99\text{m}}\text{Tc}$), rhenium-186 (^{186}Re), and rhenium-188 (^{188}Re); antibiotics, such as doxorubicin, adriamycin, daunorubicin, methotrexate, daunomycin, neocarzinostatin, and carboplatin; bacterial, plant, and other toxins, such as diphtheria toxin, pseudomonas exotoxin A, staphylococcal enterotoxin A, abrin-A toxin, ricin A (deglycosylated ricin A and native ricin A), TGF-alpha toxin, cytotoxin from chinese cobra (*naja naja atra*), and gelonin (a plant toxin); ribosome inactivating proteins from plants, bacteria and fungi, such as restrictocin (a ribosome inactivating protein produced by *Aspergillus restrictus*), saporin (a ribosome inactivating protein from *Saponaria officinalis*), and RNase; tyrosine kinase inhibitors; ly207702 (a difluorinated purine nucleoside); liposomes containing antitumor agents (*e.g.*,

antisense oligonucleotides, plasmids which encode for toxins, methotrexate, etc.); and other antibodies or antibody fragments, such as F(ab).

[104] Those of skill in the art will readily understand and be able to make such antibody derivatives, as they are well known in the art. The antibodies may be cytotoxic on their own, or they may be used to deliver cytotoxic agents to particular locations in the body. The antibodies can be administered to individuals in need thereof as a form of passive immunization.

[105] Characterization of extracellular regions for the cell surface and secreted proteins from the protein sequence is based on the prediction of signal sequence, transmembrane domains and functional domains. Antibodies are preferably specifically immunoreactive with membrane associated proteins, particularly to extracellular domains of such proteins or to secreted proteins. Such targets are readily accessible to antibodies, which typically do not have access to the interior of cells or nuclei. However, in some applications, antibodies directed to intracellular proteins may be useful as well. Moreover, for diagnostic purposes, an intracellular protein may be an equally good target since cell lysates may be used rather than a whole cell assay.

[106] Computer programs can be used to identify extracellular domains of proteins whose sequences are known. Such programs include SMART software (Schultz et al., Proc. Natl. Acad. Sci. USA 95: 5857-5864, 1998) and Pfam software (Bateman et al., Nucleic acids Res. 28: 263-266, 2000) as well as PSORTIL. Typically such programs identify transmembrane domains; the extracellular domains are identified as immediately adjacent to the transmembrane domains. Prediction of extracellular regions and the signal cleavage sites are only approximate. It may have a margin of error + or - 5 residues. Signal sequence can be predicted using three different methods (Nielsen et al, *Protein Engineering* 10: 1-6, 1997, Jagla et. al, *Bioinformatics* 16: 245-250, 2000, Nakai, K and Horton, P. *Trends in Biochem. Sci.* 24:34-35, 1999) for greater accuracy.

Similarly transmembrane (TM) domains can be identified by multiple prediction methods. (Pasquier, et. al, Protein Eng. 12:381-385, 1999, Somhammer et al., In Proc. of Sixth Int. Conf. on Intelligent Systems for Molecular Biology, p. 175-182 , Ed J. Glasgow, T. Littlejohn, F. Major, R. Lathrop, D. Sankoff, and C. Sensen Menlo Park, CA: AAAI Press, 1998 , Klein, et.al, Biochim. Biophys. Acta, 815:468, 1985, Nakai and Kanehisa Genomics, 14: 897-911 , 1992). In ambiguous cases, locations of functional domains in well characterized proteins are used as a guide to assign a cellular localization.

[107] Putative functions or functional domains of novel proteins can be inferred from homologous regions in the database identified by BLAST searches (Altschul et. al. Nucleic Acid Res. 25: 3389-3402, 1997) and/or from a conserved domain database such as Pfam (Bateman et.al, Nucleic Acids Res. 27:260-262 1999) BLOCKS (Henikoff, et. al, Nucl. Acids Res. 28:228-230, 2000) and SMART (Ponting, et. al, Nucleic Acid Res. 27,229-232, 1999). Extracellular domains include regions adjacent to a transmembrane domain in a single transmembrane domain protein (out-in or type I class). For multiple transmembrane domains proteins, the extracellular domain also includes those regions between two adjacent transmembrane domains (in-out and out-in). For type II transmembrane domain proteins, for which the N-terminal region is cytoplasmic, regions following the transmembrane domain is generally extracellular. Secreted proteins on the other hand do not have a transmembrane domain and hence the whole protein is considered as extracellular.

[108] Membrane associated proteins can be engineered to delete the transmembrane domains, thus leaving the extracellular portions which can bind to ligands. Such soluble forms of transmembrane receptor proteins can be used to compete with natural forms for binding to ligand. Thus such soluble forms act as inhibitors, and can be used therapeutically as anti-angiogenic agents, as diagnostic tools for the quantification of natural ligands, and in assays for the identification of small molecules which modulate or mimic the activity of a TEM:ligand complex.

[109] Alternatively, the endothelial markers themselves can be used as vaccines to raise an immune response in the vaccinated animal or human. For such uses, a protein, or immunogenic fragment of such protein, corresponding to the intracellular, extracellular or secreted TEM of interest is administered to a subject. The immunogenic agent may be provided as a purified preparation or in an appropriately expressing cell. The administration may be direct, by the delivery of the immunogenic agent to the subject, or indirect, through the delivery of a nucleic acid encoding the immunogenic agent under conditions resulting in the expression of the immunogenic agent of interest in the subject. The TEM of interest may be delivered in an expressing cell, such as a purified population of tumor endothelial cells or a populations of fused tumor endothelial and dendritic cells. Nucleic acids encoding the TEM of interest may be delivered in a viral or non-viral delivery vector or vehicle. Non-human sequences encoding the human TEM of interest or other mammalian homolog can be used to induce the desired immunologic response in a human subject. For several of the TEMs of the present invention, mouse, rat or other ortholog sequences are described herein or can be obtained from the literature or using techniques well within the skill of the art.

[110] Endothelial cells can be identified using the markers which are disclosed herein as being endothelial cell specific. These include the human markers identified by SEQ ID NOS: 1-172, *i.e.*, the normal, pan-endothelial, and the tumor endothelial markers. Homologous mouse markers include tumor endothelial markers of SEQ ID NO: 182-186 and 190-194. Antibodies specific for such markers can be used to identify such cells, by contacting the antibodies with a population of cells containing some endothelial cells. The presence of cross-reactive material with the antibodies identifies particular cells as endothelial. Similarly, lysates of cells can be tested for the presence of cross-reactive material. Any known format or technique for detecting cross-reactive material can be used including, immunoblots, radioimmunoassay, ELISA, immunoprecipitation, and

immunohistochemistry. In addition, nucleic acid probes for these markers can also be used to identify endothelial cells. Any hybridization technique known in the art including Northern blotting, RT-PCR, microarray hybridization, and in situ hybridization can be used.

- [111] One can identify tumor endothelial cells for diagnostic purposes, testing cells suspected of containing one or more TEMs. One can test both tissues and bodily fluids of a subject. For example, one can test a patient's blood for evidence of intracellular and membrane associated TEMs, as well as for secreted TEMs. Intracellular and/or membrane associated TEMs may be present in bodily fluids as the result of high levels of expression of these factors and/or through lysis of cells expressing the TEMs.
- [112] Populations of various types of endothelial cells can also be made using the antibodies to endothelial markers of the invention. The antibodies can be used to purify cell populations according to any technique known in the art, including but not limited to fluorescence activated cell sorting. Such techniques permit the isolation of populations which are at least 50, 60, 70, 80, 90, 92, 94, 95, 96, 97, 98, and even 99 % the type of endothelial cell desired, whether normal, tumor, or pan-endothelial. Antibodies can be used to both positively select and negatively select such populations. Preferably at least 1, 5, 10, 15, 20, or 25 of the appropriate markers are expressed by the endothelial cell population.
- [113] Populations of endothelial cells made as described herein, can be used for screening drugs to identify those suitable for inhibiting the growth of tumors by virtue of inhibiting the growth of the tumor vasculature.
- [114] Populations of endothelial cells made as described herein, can be used for screening candidate drugs to identify those suitable for modulating angiogenesis, such as for inhibiting the growth of tumors by virtue of inhibiting the growth of endothelial cells, such as inhibiting the growth of the tumor or other undesired

vasculature, or alternatively, to promote the growth of endothelial cells and thus stimulate the growth of new or additional large vessel or microvasculature.

- [115] Inhibiting the growth of endothelial cells means either regression of vasculature which is already present, or the slowing or the absence of the development of new vascularization in a treated system as compared with a control system. By stimulating the growth of endothelial cells, one can influence development of new (neovascularization) or additional vasculature development (revascularization). A variety of model screen systems are available in which to test the angiogenic and/or anti-angiogenic properties of a given candidate drug. Typical tests involve assays measuring the endothelial cell response, such as proliferation, migration, differentiation and/or intracellular interaction of a given candidate drug. By such tests, one can study the signals and effects of the test stimuli. Some common screens involve measurement of the inhibition of heparanase, endothelial tube formation on Matrigel, scratch induced motility of endothelial cells, platelet-derived growth factor driven proliferation of vascular smooth muscle cells, and the rat aortic ring assay (which provides an advantage of capillary formation rather than just one cell type).
- [116] Drugs can be screened for the ability to mimic or modulate, inhibit or stimulate, growth of tumor endothelium cells and/or normal endothelial cells. Drugs can be screened for the ability to inhibit tumor endothelium growth but not normal endothelium growth or survival. Similarly, human cell populations, such as normal endothelium populations or tumor endothelial cell populations, can be contacted with test substances and the expression of tumor endothelial markers and/or normal endothelial markers determined. Test substances which decrease the expression of tumor endothelial markers (TEMs) are candidates for inhibiting angiogenesis and the growth of tumors. Conversely, markers which are only expressed in normal endothelium but not in tumor endothelium (NEMs) can be monitored. Test substances which increase the expression of such NEMs in tumor endothelium and other human cells can be identified as candidate antitumor or

anti-angiogenic drugs In cases where the activity of a TEM or NEM is known, agents can be screened for their ability to decrease or increase the activity.

- [117] For those tumor endothelial markers identified as containing transmembrane regions, it is desirable to identify drug candidates capable of binding to the TEM receptors found at the cell surface. For some applications, the identification of drug candidates capable of blocking the TEM receptor from its native ligand will be desired. For some applications, the identification of a drug candidate capable of binding to the TEM receptor may be used as a means to deliver a therapeutic or diagnostic agent. For other applications, the identification of drug candidates capable of mimicing the activity of the native ligand will be desired. Thus, by manipulating the binding of a transmembrane TEM receptor:ligand complex, one may be able to promote or inhibit further development of endothelial cells and hence, vascularization.
- [118] For those tumor endothelial markers identified as being secreted proteins, it is desirable to identify drug candidates capable of binding to the secreted TEM protein. For some applications, the identification of drug candidates capable of interfering with the binding of the secreted TEM to its native receptor. For other applications, the identification of drug candidates capable of mimicing the activity of the native receptor will be desired. Thus, by manipulating the binding of the secreted TEM:receptor complex, one may be able to promote or inhibit further development of endothelial cells, and hence, vascularization.
- [119] Expression can be monitored according to any convenient method. Protein or mRNA can be monitored. Any technique known in the art for monitoring specific genes' expression can be used, including but not limited to ELISAs, SAGE, microarray hybridization, Western blots. Changes in expression of a single marker may be used as a criterion for significant effect as a potential pro-angiogenic, anti-angiogenic or anti-tumor agent. However, it also may be desirable to screen for test substances which are able to modulate the expression

of at least 5, 10, 15, or 20 of the relevant markers, such as the tumor or normal endothelial markers. Inhibition of TEM protein activity can also be used as a drug screen. Human and mouse TEMS can be used for this purpose.

[120] Test substances for screening can come from any source. They can be libraries of natural products, combinatorial chemical libraries, biological products made by recombinant libraries, etc. The source of the test substances is not critical to the invention. The present invention provides means for screening compounds and compositions which may previously have been overlooked in other screening schemes. Nucleic acids and the corresponding encoded proteins of the markers of the present invention can be used therapeutically in a variety of modes. NEMs, can be used to restrict, diminish, reduce, or inhibit proliferation of tumor or other abnormal or undesirable vasculature. TEMs can be used to stimulate the growth of vasculature, such as for wound healing or to circumvent a blocked vessel. The nucleic acids and encoded proteins can be administered by any means known in the art. Such methods include, using liposomes, nanospheres, viral vectors, non-viral vectors comprising polycations, etc. Suitable viral vectors include adenovirus, retroviruses, and sindbis virus. Administration modes can be any known in the art, including parenteral, intravenous, intramuscular, intraperitoneal, topical, intranasal, intrarectal, intrabronchial, etc.

[121] Specific biological antagonists of TEMs can also be used to therapeutic benefit. For example, antibodies, T cells specific for a TEM, antisense to a TEM, and ribozymes specific for a TEM can be used to restrict, inhibit, reduce, and/or diminish tumor or other abnormal or undesirable vasculature growth. Such antagonists can be administered as is known in the art for these classes of antagonists generally. Anti-angiogenic drugs and agents can be used to inhibit tumor growth, as well as to treat diabetic retinopathy, rheumatoid arthritis, psoriasis, polycystic kidney disease (PKD), and other diseases requiring angiogenesis for their pathologies.

- [122] Mouse counterparts to human TEMS can be used in mouse cancer models or in cell lines or *in vitro* to evaluate potential anti-angiogenic or anti-tumor compounds or therapies. Their expression can be monitored as an indication of effect. Mouse TEMs are disclosed in SEQ ID NO: 182-186 and 190-194. Mouse TEMs can be used as antigens for raising antibodies which can be tested in mouse tumor models. Mouse TEMs with transmembrane domains are particularly preferred for this purpose. Mouse TEMs can also be used as vaccines to raise an immunological response in a human to the human ortholog.
- [123] The above disclosure generally describes the present invention. All references disclosed herein are expressly incorporated by reference. A more complete understanding can be obtained by reference to the following specific examples which are provided herein for purposes of illustration only, and are not intended to limit the scope of the invention.

EXAMPLE 1

Visualization of vasculature of colorectal cancers

- [124] The endothelium of human colorectal cancer was chosen to address the issues of tumor angiogenesis, based on the high incidence, relatively slow growth, and resistance to anti-neoplastic agents of these cancers. While certain less common tumor types, such as glioblastomas, are highly vascularized and are regarded as good targets for anti-angiogenic therapy, the importance of angiogenesis for the growth of human colorectal cancers and other common solid tumor types is less well documented.
- [125] We began by staining vessels in colorectal cancers using von Willebrand Factor (vWF) as a marker. In each of 6 colorectal tumors, this examination revealed a high density of vessels throughout the tumor parenchyma (Examples in Fig. 1 A and B). Interestingly, these analyses also substantiated the importance of these

vessels for tumor growth, as endothelium was often surrounded by a perivascular cuff of viable cells, with a ring of necrotic cells evident at the periphery (Example in Fig. 1A). Although these preliminary studies suggested that colon tumors are angiogenesis-dependent, reliable markers that could distinguish vessels in colon cancers from the vessels in normal colon are currently lacking. One way to determine if such markers exist is by analyzing gene expression profiles in endothelium derived from normal and neoplastic tissue.

EXAMPLE 2

Purification of endothelial cells

[126] Global systematic analysis of gene expression in tumor and normal endothelium has been hampered by at least three experimental obstacles. First, endothelium is enmeshed in a complex tissue consisting of vessel wall components, stromal cells, and neoplastic cells, requiring highly selective means of purifying ECs for analysis. Second, techniques for defining global gene expression profiles were not available until recently. And third, only a small fraction of the cells within a tumor are endothelial, mandating the development of methods that are suitable for the analysis of global expression profiles from relatively few cells.

[127] To overcome the first obstacle, we initially attempted to purify ECs from dispersed human colorectal tissue using CD31, an endothelial marker commonly used for this purpose. This resulted in a substantial enrichment of ECs but also resulted in contamination of the preparations by hematopoietic cells, most likely due to expression of CD31 by macrophages. We therefore developed a new method for purifying ECs from human tissues using P1H12, a recently described marker for ECs. Unlike CD31, P1H12 was specifically expressed on the ECs of both colorectal tumors and normal colorectal mucosa. Moreover, immunofluorescence staining of normal and cancerous colon with a panel of known cell surface endothelial markers (e.g. VE-cadherin, CD31 and CD34)

revealed that P1H12 was unique in that it stained all vessels including microvessels (see Fig. 2A and data not shown). In addition to selection with P1H12, it was necessary to optimize the detachment of ECs from their neighbors without destroying their cell surface proteins as well as to employ positive and negative affinity purifications using a cocktail of antibodies (Fig. 2B). The ECs purified from normal colorectal mucosa and colorectal cancers were essentially free of epithelial and hematopoietic cells as judged by RT-PCR (Fig. 2C) and subsequent gene expression analysis (see below).

EXAMPLE 3

Comparison of tumor and normal endothelial cell expression patterns

[128] To overcome the remaining obstacles, a modification of the Serial Analysis of Gene Expression (SAGE) technique was used. SAGE associates individual mRNA transcripts with 14 base pair tags derived from a specific position near their 3' termini. The abundance of each tag provides a quantitative measure of the transcript level present within the mRNA population studied. SAGE is not dependent on pre-existing databases of expressed genes, and therefore provides an unbiased view of gene expression profiles. This feature is particularly important in the analysis of cells that constitute only a small fraction of the tissue under study, as transcripts from these cells are unlikely to be well represented in extant EST databases. We adapted the SAGE protocol so that it could be used on small numbers of purified ECs obtained from the procedure outlined in Fig. 2B. A library of ~100,000 tags from the purified ECs of a colorectal cancer, and a similar library from the ECs of normal colonic mucosa from the same patient were generated. These ~193,000 tags corresponded to over 32,500 unique transcripts. Examination of the expression pattern of hematopoietic, epithelial and endothelial markers confirmed the purity of the preparations (Fig. 2D).

EXAMPLE 4**Markers of normal and tumor endothelium**

[129] We next sought to identify Pan Endothelial Markers (PEMs), that is, transcripts that were expressed at significantly higher levels in both normal and tumor associated endothelium compared to other tissues. To identify such PEMs, tags expressed at similar levels in both tumor and normal ECs were compared to ~ 1.8 million tags from a variety of cell lines derived from tumors of non-endothelial origin. This simple comparison identified 93 transcripts that were strikingly EC-specific, i.e. expressed at levels at least 20-fold higher in ECs in vivo compared to non-endothelial cells in culture. The 15 tags corresponding to characterized genes which were most highly and specifically expressed in endothelium are shown in Table 1A. Twelve of these 15 most abundant endothelial transcripts had been previously shown to be preferentially expressed in endothelium, while the other 3 genes had not been associated with endothelium in the past (Table 1A). These data sets also revealed many novel PEMs, which became increasingly prevalent as tag expression levels decreased (Table 1B). For many of the transcripts, their endothelial origin was confirmed by SAGE analysis of ~401,000 transcripts derived from primary cultures of human umbilical vein endothelial cells (HUVEC) and human dermal microvascular endothelial cells (HMVEC) (Table 1 A and B). To further validate the expression of these PEMs in vivo, we developed a highly sensitive non-radioactive in situ hybridization method that allowed the detection of transcripts expressed at relatively low levels in frozen sections of human tissues. Two uncharacterized markers, PEM3 and PEM6, were chosen for this analysis. In each case, highly specific expression was clearly limited to vascular ECs in both normal and neoplastic tissues (Fig. 3 A and B and data not shown). These data also suggest that ECs maintained in culture do not completely recapitulate expression patterns observed in vivo. For example, Hevin and several other PEM's were expressed at high levels in both tumor and normal

ECs in vivo, but few or no transcripts were detected in cultured HUVEC or HMVEC (Table 1). The source of the Hevin transcripts was confirmed to be endothelium by in situ hybridization in normal and malignant colorectal tissue (Fig. 3C).

- [130] Many of the markers reported in Table 1 were expressed at significantly higher levels than previously characterized genes commonly associated with ECs. For example, the top 25 markers were all expressed at greater than 200 copies per cell. In contrast, the receptors for VEGF (VEGFR-1 and VEGFR-2) were expressed at less than 20 copies per cell. Interestingly, VEGFR2 (KDR), which had previously been reported to be up-regulated in vessels during colon cancer progression, was found to be expressed in both normal and neoplastic colorectal tissue (Fig. 3 D and E). The lack of specificity of this gene was in accord with the SAGE data, which indicated that the VEGFR was expressed at 12 copies per cell in both normal and tumor endothelium.

EXAMPLE 5

Tumor *versus* normal endothelium

- [131] We next attempted to identify transcripts that were differentially expressed in endothelium derived from normal or neoplastic tissues. This comparison revealed 33 tags that were preferentially expressed in normal-derived endothelium at levels at least 10-fold higher than in tumor-derived endothelium. Conversely, 46 tags were expressed at 10-fold or higher levels in tumor vessels. Because those transcripts expressed at higher levels in tumor endothelium are most likely to be useful in the future for diagnostic and therapeutic purposes, our subsequent studies focussed on this class. Of the top 25 tags most differentially expressed, 12 tags corresponded to 11 previously identified genes, one with an alternative polyadenylation site (see Table 2). Of these 10 genes, 6 have been recognized as markers associated with angiogenic vessels. The remaining 14 tags corresponded

to uncharacterised genes, most of which have only been deposited as ESTs (Table 2).

[132] To validate the expression patterns of these genes, we chose to focus on 9 Tumor Endothelial Markers (BSC-TEM 1-9; TEM 1, 2, 5, 9, 16, 17, 19, and 22) for which EST sequences but no other information was available (Table 2). These tags were chosen simply because they were among the most differentially expressed on the list and because we were able to obtain suitable probes. In many cases, this required obtaining near full-length sequences through multiple rounds of sequencing and cDNA walking (See accession numbers in Table 2). RT-PCR analysis was then used to evaluate the expression of the corresponding transcripts in purified ECs derived from normal and tumor tissues of two patients different from the one used to construct the SAGE libraries. As shown in Fig. 4 A, the vWF gene, expected to be expressed in both normal and tumor endothelium on the basis of the SAGE data as well as previous studies, was expressed at similar levels in normal and tumor ECs from both patients, but was not expressed in purified tumor epithelial cells. As expected, PEM2 displayed a pattern similar to vWF. In contrast, all 9 TEMs chosen for this analysis were prominently expressed in tumor ECs, but were absent or barely detectable in normal ECs (Table 3 and examples in Fig. 4A). It is important to note that these RT-PCR assays were extremely sensitive indicators of expression, and the absence of detectable transcripts in the normal endothelium, combined with their presence in tumor endothelial RNAs even when diluted 100-fold, provides compelling confirmatory evidence for their differential expression. These results also show that these transcripts were not simply expressed differentially in the ECs of the original patient, but were characteristic of colorectal cancer endothelium in general.

[133] It could be argued that the results noted above were compromised by the possibility that a small number of non-endothelial cells contaminated the cell populations used for SAGE and RT-PCR analyses, and that these non-endothelial

cells were responsible for the striking differences in expression of the noted transcripts. To exclude this possibility, we performed in situ hybridization on normal and neoplastic colon tissue. In every case where transcripts could be detected (BSC-TEM 1, 3, 4, 5, 7, 8, and 9; TEM 1, 5, 9, 17, and 19), they were specifically localized to ECs (Table 3 and examples in Fig. 4 B and C). Although caution must be used when interpreting negative in situ hybridization results, none of the TEMs were expressed in vascular ECs associated with normal colorectal tissue even though vWF and Hevin were clearly expressed (Table 3).

EXAMPLE 6

Tumor endothelium markers are expressed in multiple tumor types

[134] Were these transcripts specifically expressed in the endothelium within primary colorectal cancers, or were they characteristic of tumor endothelium in general? To address this question, we studied the expression of a representative TEM (BSC-TEM7; TEM 17) in a liver metastasis from a colorectal cancer, a sarcoma, and in primary cancers of the lung, pancreas, breast and brain. As shown in Fig. 4, the transcript was found to be expressed specifically in the endothelium of each of these cancers, whether metastatic (Fig. 4D) or primary (Fig. 4E-I). Analysis of the other six TEMs, (BSC-TEM 1, 3, 4, 5, 7, 8 and 9; TEM 1, 5, 9, 17, and 19) revealed a similar pattern in lung tumors, brain tumors, and metastatic lesions of the liver (see Table 3).

EXAMPLE 7

Tumor endothelium markers are neo-angiogenic

[135] Finally, we asked whether these transcripts were expressed in angiogenic states other than that associated with tumorigenesis. We thus performed in situ hybridizations on corpus luteum tissue as well as healing wounds. Although there

were exceptions, we found that these transcripts were generally expressed both in the corpus luteum and in the granulation tissue of healing wounds (Table 3 and example in Fig. 4J). In all tissues studied, expression of the genes was either absent or exclusively confined to the EC compartment.

References and Notes

The disclosure of each reference cited is expressly incorporated herein.

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8. The original EC isolation protocol was the same as that shown in Fig. 2B except that dispersed cells were stained with anti-CD31 antibodies instead of anti-PIH12, and magnetic beads against CD64 and CD14 were not included in the negative selection. After generating 120,000 SAGE tags from these two EC preparations, careful analysis of the SAGE data revealed that, in addition to endothelial-specific markers, several macrophage-specific markers were also present.
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11. In order to reduce the minimum amount of starting material required from ~50 million cells to ~50,000 cells (i.e. ~1000-fold less) we and others (38) have introduced

several modifications to the original SAGE protocol. A detailed version of our modified "MicroSAGE" protocol is available from the authors upon request.

12. 96,694 and 96,588 SAGE tags were analyzed from normal and tumor derived ECs, respectively, and represented 50,298 unique tags. A conservative estimate of 32,703 unique transcripts was derived by considering only those tags observed more than once in the current data set or in the 134,000 transcripts previously identified in human transcriptomes (39).

13. To identify endothelial specific transcripts, we normalized the number of tags analyzed in each group to 100,000, and limited our analysis to transcripts that were expressed at levels at least 20-fold higher in ECs than in non-endothelial cell lines in culture and present at fewer than 5 copies per 100,000 transcripts in non-endothelial cell lines and the hematopoietic fraction (~57,000 tags)(41). Non-endothelial cell lines consisted of 1.8x10⁶ tags derived from a total of 14 different cancer cell lines including colon, breast, lung, and pancreatic cancers, as well as one non-transformed keratinocyte cell line, two kidney epithelial cell lines, and normal monocytes. A complete list of PEMs is available at www.sagenet.org/angio/table1.htm.

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26. For non-radioactive in situ hybridization, digoxigenin (DIG)-labelled sense and anti-sense riboprobes were generated through PCR by amplifying 500-600 bp products and incorporating a T7 promoter into the anti-sense primer. In vitro transcription was performed using DIG RNA labelling reagents and T7 RNA polymerase (Roche, Indianapolis, IN). Frozen tissue sections were fixed with 4 % paraformaldehyde, permeabilized with pepsin, and incubated with 200 ng/ml of riboprobe overnight at 55°C. For signal amplification, a horseradish peroxidase (HRP) rabbit anti-DIG antibody (DAKO, Carpinteria, CA) was used to catalyse the deposition of Biotin-Tyramide (from GenPoint kit, DAKO). Further amplification was achieved by adding HRP rabbit anti-biotin (DAKO), biotin-tyramide, and then alkaline-phosphatase (AP) rabbit anti-biotin (DAKO). Signal was detected using the AP substrate Fast Red TR/Naphthol AS-MX (Sigma, St. Louis, MO), and cells were counterstained with hematoxylin unless otherwise indicated. A detailed protocol including the list of primers used to generate the probes can be obtained from the authors upon request.
27. Transcript copies per cell were calculated assuming an average cell contains 300,000 transcripts.

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31. Endothelial-specific transcripts were defined as those expressed at levels at least 5-fold higher in ECs in vivo than in non-endothelial cell lines in culture (13), and present at no more than 5 copies per 100,000 transcripts in non-endothelial cell lines and the hematopoietic cell fraction (41). Transcripts showing statistically different levels of expression ($P < 0.05$) were then identified using Monte Carlo analysis as previously described (40). Transcripts preferentially expressed in normal endothelium were then defined as those expressed at levels at least 10-fold higher in normal endothelium than in tumor endothelium. Conversely, tumor endothelial transcripts were at least 10-fold higher in tumor versus normal endothelium. See www.sagenet.org/angio/table2.htm and www.sagenet.org/angio/table3.htm for a complete list of differentially expressed genes.
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Sequence name	SEQ ID NO:
PEM 1	1
PEM 2	2
PEM 3	3
PEM 4	4
PEM 5	5
PEM 6	6
PEM 7	7
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mTEM 5 DNA	183
mTEM 7 DNA	184
mTEM 7B DNA	185
mTEM 8 DNA	186
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TEM 5 Protein	188
TEM 7B Protein	189
mTEM 1 Protein	190
mTEM 5 Protein	191

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175	TEM 7 DNA
176	TEM 8 DNA
177	TEM 1 Protein
178	TEM 2 Protein
179	TEM 8 Protein
180	TEM 5 DNA
181	TEM 7B DNA
182	mTEM 1 DNA
183	mTEM 5 DNA
184	mTEM 7 DNA
185	mTEM 7B DNA
186	mTEM 8 DNA
187	TEM 8 Protein
188	TEM 5 Protein
189	TEM 7B Protein
190	mTEM 1 Protein
191	mTEM 5 Protein

mTEM 7 Protein	192
mTEM 7b Protein	193
mTEM 8 Protein	194
TEM 1 DNA	195
TEM 1 Protein	196
TEM 2 DNA	197
TEM 2 Protein	198
TEM 3 DNA	199
TEM 3 Protein	200
TEM 4 DNA	201
TEM 4 Protein	202
TEM 5 DNA	203
TEM 5 Protein	204
TEM 6 DNA	205
TEM 6 Protein	206
TEM 7 DNA	207
TEM 7 Protein	208
TEM 8 DNA	209
TEM 8 Protein	210
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TEM 9 Protein	212
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TEM 10 Protein	214
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TEM 11 Protein	216
TEM 12 DNA	217
TEM 12 Protein	218
TEM 13 DNA	219
TEM 13 Protein	220
TEM 14a DNA	221
TEM 14b DNA	222
TEM 14a Protein	223
TEM 14b Protein	224
TEM 15 DNA	225
TEM 15 Protein	226
TEM 16 DNA	227
TEM 16 Protein	228
TEM 17 DNA	229
TEM 17 Protein	230

192	mTEM 7 Protein
193	mTEM 7b Protein
194	mTEM 8 Protein
195	TEM 1 DNA
196	TEM 1 Protein
197	TEM 2 DNA
198	TEM 2 Protein
199	TEM 3 DNA
200	TEM 3 Protein
201	TEM 4 DNA
202	TEM 4 Protein
203	TEM 5 DNA
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223	TEM 14a Protein
224	TEM 14b Protein
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TEM 20 DNA	233
TEM 20 Protein	234
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TEM 39 Protein	263
TEM 40 DNA	264
TEM 40 Protein	265
TEM 41 DNA	266
TEM 41 Protein	267
TEM 42 DNA	268

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233	TEM 20 DNA
234	TEM 20 Protein
235	TEM 21 DNA
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237	TEM 22 DNA
238	TEM 22 Protein
239	TEM 24 DNA
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262	TEM 39 DNA
263	TEM 39 Protein
264	TEM 40 DNA
265	TEM 40 Protein
266	TEM 41 DNA
267	TEM 41 Protein
268	TEM 42 DNA
269	TEM 42 Protein

TEM 42 Protein	269
TEM 44 DNA	270
TEM 44 Protein	271
TEM 45 DNA	272
TEM 45 Protein	273
TEM 46 DNA	274
TEM 46 Protein	275
NEM 4 DNA	276
NEM 4 Protein	277
NEM 14 DNA	278
NEM 14 Protein	279
NEM 17 DNA	280
NEM 17 Protein	281
NEM 22 DNA	282
NEM 22 Protein	283
NEM 23 DNA	284
NEM 23 Protein	285
NEM 23 Secreted	286
NEM 23 Short	287
NEM 33 DNA	288
NEM 33 Protein	289
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mTEM 1 Protein	291
mTEM 2 DNA	292
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mTEM 3 Protein	299
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mTEM 30 Protein	307

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273	TEM 45 Protein
274	TEM 46 DNA
275	TEM 46 Protein
276	NEM 4 DNA
277	NEM 4 Protein
278	NEM 14 DNA
279	NEM 14 Protein
280	NEM 17 DNA
281	NEM 17 Protein
282	NEM 22 DNA
283	NEM 22 Protein
284	NEM 23 DNA
285	NEM 23 Protein
286	NEM 23 Secreted
287	NEM 23 Short
288	NEM 33 DNA
289	NEM 33 Protein
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291	mTEM 1 Protein
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293	mTEM 2 Protein
294	mTEM 9 DNA
295	mTEM 9 Protein
296	mTEM 17 DNA
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298	mTEM 3 DNA
299	mTEM 3 Protein
300	mTEM 19 DNA
301	mTEM 19 Protein
302	mTEM 13 DNA
303	mTEM 13 Protein
304	mTEM 22 DNA
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306	mTEM 30 DNA
307	mTEM 30 Protein
308	TEM 2 tag

TEM 2 tag	308
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TEM 5 long tag	312
TEM 5 long tag	313
TEM 6 long tag	314
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347	TEM 37 long tag

TEM 37 long tag	347
TEM 38 long tag	348
TEM 38 long tag	349
TEM 39 long tag	350
TEM 40 long tag	351
TEM 41 long tag	352
TEM 42 long tag	353
TEM 43 long tag	354
TEM 44 long tag	355
TEM 45 long tag	356
TEM 46 long tag	357

348	TEM 38 long tag
349	TEM 38 long tag
350	TEM 39 long tag
351	TEM 40 long tag
352	TEM 41 long tag
353	TEM 42 long tag
354	TEM 43 long tag
355	TEM 44 long tag
356	TEM 45 long tag
357	TEM 46 long tag
358	TEM 35 Protein

CLAIMS

1. An isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 9, 17, 19, and 44, as shown in SEQ ID NO: 196, 212, 230, 232, and 271, respectively.
2. The isolated molecule of claim 1 which is an intact antibody molecule.
3. The isolated molecule of claim 1 which is a single chain variable region (ScFv).
4. The isolated molecule of claim 1 which is a monoclonal antibody.
5. The isolated molecule of claim 1 which is a humanized antibody.
6. The isolated molecule of claim 1 which is a human antibody.
7. The isolated molecule of claim 1 which is bound to a cytotoxic moiety.
8. The isolated molecule of claim 1 which is bound to a therapeutic moiety.
9. The isolated molecule of claim 1 which is bound to a detectable moiety.
10. The isolated molecule of claim 1 which is bound to an anti-tumor agent.

11. A method of inhibiting neoangiogenesis, comprising:
administering to a subject in need thereof an effective amount of an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 9, 17, 19, 22, and 44, as shown in SEQ ID NO: 196, 212, 230, 232, 238, and 271, respectively, whereby neoangiogenesis is inhibited.
12. The method of claim 11 wherein the subject bears a vascularized tumor.
13. The method of claim 11 wherein the subject has polycystic kidney disease.
14. The method of claim 11 wherein the subject has diabetic retinopathy.
15. The method of claim 11 wherein the subject has rheumatoid arthritis.
16. The method of claim 11 wherein the subject has psoriasis.

17. A method of inhibiting tumor growth, comprising:

administering to a human subject bearing a tumor an effective amount of an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 9, 17, 19, 22, and 44, as shown in SEQ ID NO: 196, 212, 230, 232, 238, and 271, respectively, whereby growth of the tumor is inhibited.

18. An isolated molecule comprising an antibody variable region which specifically binds to a TEM protein selected from the group consisting of: 9, 17, 19, and 44, as shown in SEQ ID NO: 212, 230, 232, and 271, respectively.

19. The isolated molecule of claim 18 which is a single chain variable region (ScFv).

20. The isolated molecule of claim 18 which is a monoclonal antibody.

21. The isolated molecule of claim 18 which is a humanized antibody.

22. The isolated molecule of claim 18 which is a human antibody.

23. The isolated molecule of claim 18 which is bound to a cytotoxic moiety.

24. The isolated molecule of claim 18 which is bound to a therapeutic moiety.

25. The isolated molecule of claim 18 which is bound to a detectable

moiety.

26. The isolated molecule of claim 18 which is bound to an anti-tumor agent.
27. The isolated molecule of claim 18 which is an intact antibody molecule.
28. An isolated and purified human transmembrane protein selected from the group consisting of: TEM 9, 17, and 19 as shown in SEQ ID NO: 212, 230, and 232, respectively.
29. An isolated and purified nucleic acid molecule comprising a coding sequence for a transmembrane TEM selected from the group consisting of: TEM 9, 17, and 19 as shown in SEQ ID NO: 212, 230, 232, respectively.
30. The isolated and purified nucleic acid molecule of claim 29 which comprises a coding sequence selected from those shown in SEQ ID NO: 211, 229, and 231,.
31. A recombinant host cell which comprises a nucleic acid molecule comprising a coding sequence for a transmembrane TEM selected from the group consisting of: TEM 9, 17, and 19 as shown in SEQ ID NO: 212, 230, and 232, respectively.
32. The recombinant host cell of claim 31 which comprises a coding sequence selected from those shown in SEQ ID NO: 211, 229, and 231.
33. A method of inducing an immune response in a mammal, comprising:
administering to the mammal a nucleic acid molecule comprising a coding sequence for a human transmembrane protein selected from the group consisting of: TEM 1, 9, 13, 17, 19, 22, 30, and 44 as shown in SEQ ID NO: 196, 212, 220, 230, 232, 238, 250 and 271, respectively, whereby an immune response to the human transmembrane protein is induced in the mammal.

34. The method of claim 33 wherein the coding sequence is shown in SEQ ID NO: 195, 211, 219, 229, 231, 237, 249, 270.

35. A method of inducing an immune response in a mammal, comprising:

administering to the mammal a purified human transmembrane protein selected from the group consisting of: TEM 1, 9, 13, 17, 19, 22, 30, and 44 as shown in SEQ ID NO: 196, 212, 220, 230, 232, 238, 250 and 271, respectively, whereby an immune response to the human transmembrane protein is induced in the mammal.

36. A method for identification of a ligand involved in endothelial cell regulation, comprising:

contacting a test compound with an isolated and purified human transmembrane protein selected from the group consisting of 1, 9, 13, 17, 19, 30, and 44 as shown in SEQ ID NO: 196, 212, 220, 230, 250, 232 and 271;

contacting the isolated and purified human transmembrane protein with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 9, 13, 17, 19, 30, and 44 as shown in SEQ ID NO: 196, 212, 220, 230, 250, 232 and 271, respectively;

determining binding of the molecule comprising an antibody variable region to the human transmembrane protein, wherein a test compound which diminishes the binding of the molecule comprising an antibody variable region to the human transmembrane protein is identified as a ligand involved in endothelial cell regulation.

37. A method for identification of a ligand involved in endothelial cell regulation, comprising:

contacting a test compound with a cell comprising a human transmembrane protein selected from the group consisting of 1, 9, 17, and 19 as shown in SEQ ID NO: 196, 212, 230, and 232;

contacting the cell with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 9, 17, and 19 as shown in SEQ ID NO: 196, 212, 230, and 232, respectively;

determining binding of the molecule comprising an antibody variable region to the cell, wherein a test compound which diminishes the binding of the molecule comprising an antibody variable region to the cell is identified as a ligand involved in endothelial cell regulation.

38. A soluble form of a human transmembrane protein selected from the group consisting of: TEM 1, 9, 17, 19, 22, 30 and 44 as shown in SEQ ID NO: 196, 212, 230, 232, 238, 250, and 271, respectively, wherein the soluble forms lack transmembrane domains.

39. The soluble form of claim 38 wherein the soluble form consists of an extracellular domain of the human transmembrane protein.

40. A method of inhibiting neoangiogenesis in a patient, comprising: administering to the patient a soluble form of a human transmembrane protein according to claim 38, whereby neoangiogenesis in the patient is inhibited.

41. A method of inhibiting neoangiogenesis in a patient, comprising: administering to the patient a soluble form of a human transmembrane protein according to claim 39, whereby neoangiogenesis in the patient is inhibited.

42. The method of claim 40 wherein the patient bears a vascularized tumor.

43. The method of claim 41 wherein the patient bears a vascularized tumor.

44. The method of claim 40 wherein the patient has polycystic kidney disease.
45. The method of claim 40 wherein the patient has diabetic retinopathy.
46. The method of claim 40 wherein the patient has rheumatoid arthritis.
47. The method of claim 40 wherein the patient has psoriasis.
48. The method of claim 41 wherein the patient has polycystic kidney disease.
49. The method of claim 41 wherein the patient has diabetic retinopathy.
50. The method of claim 41 wherein the patient has rheumatoid arthritis.
51. The method of claim 41 wherein the patient has psoriasis.
52. A method of identifying regions of neoangiogenesis in a patient, comprising:
administering to a patient a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 9, 13, 17, 19, 22, 30, and 44, as shown in SEQ ID NO: 196, 212, 220, 230, 232, 238, 250, and 271, respectively, wherein the molecule is bound to a detectable moiety; and
detecting the detectable moiety in the patient, thereby identifying neoangiogenesis.
53. A method of screening for neoangiogenesis in a patient, comprising:

contacting a body fluid collected from the patient with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 9, 17, 19, and 44, as shown in SEQ ID NO: 196, 212, 230, 232, and 271, respectively, wherein detection of cross-reactive material in the body fluid with the molecule indicates neoangiogenesis in the patient.

54. A method of screening for neoangiogenesis in a patient, comprising:

contacting a body fluid collected from the patient with a molecule comprising an antibody variable region which specifically binds to a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 25, 27, 31, 36, 37, 38, 39, as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 & 224, 242, 244, 252, 257, 259, 261, and 263, respectively, wherein detection of cross-reactive material in the body fluid with the molecule indicates neoangiogenesis in the patient.

55. A method of promoting neoangiogenesis in a patient, comprising:

administering to a patient in need of neoangiogenesis a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 & 224, 234, 242, 244, 252, 257, 259, 261, 263, and 265, whereby neoangiogenesis in the patient is stimulated.

56. A method of promoting neoangiogenesis in a patient, comprising:

administering to a patient in need of neoangiogenesis a nucleic acid molecule encoding a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 & 224, 234, 242, 244, 252, 257, 259, 261, 263, and 265, whereby the TEM protein is expressed and neoangiogenesis in the patient is stimulated.

57. A method of screening for neoangiogenesis in a patient, comprising:

detecting a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 & 224, 234, 242, 244, 252, 257, 259, 261, 263, and 265, respectively, in a body fluid collected from the patient, wherein detection of the TEM protein indicates neoangiogenesis in the patient.

58. A method of screening for neoangiogenesis in a patient, comprising:

detecting in a body fluid collected from the patient a nucleic acid encoding a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, wherein the nucleic acid is selected from the group consisting of those shown in SEQ ID NO: 201, 205, 207, 213, 217, 221 & 222, 233, 241, 243, 251, 256, 258, 260, 262, and 264, respectively, wherein detection of the TEM protein indicates neoangiogenesis in the patient.

59. An isolated and purified nucleic acid molecule which encodes a NEM protein selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289.

60. The nucleic acid molecule of claim 60 wherein the nucleic acid molecule comprises a coding sequence as shown in SEQ ID NO: 278, 282, 284, and 288.

61. A recombinant host cell which comprises a nucleic acid according to claim 60.

62. An isolated and purified NEM protein selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, respectively.

63. An isolated molecule comprising an antibody variable region which specifically binds to a NEM protein selected from the group

consisting of: 14, 22, 23, and 33, as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289.

64. A method of inhibiting neoangiogenesis, comprising:

administering to a subject in need thereof an effective amount of a NEM protein selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, whereby neoangiogenesis is inhibited.

65. A method to identify candidate drugs for treating tumors, comprising:

contacting cells which express one or more TEM genes selected from the group consisting of: 1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 30, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 195, 197, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221 & 222, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 256, 258, 260, 262, 266, 268, 270, 272, and 274, respectively, with a test compound;

determining expression of said one or more TEM genes by hybridization of mRNA of said cells to a nucleic acid probe which is complementary to said mRNA; and

identifying a test compound as a candidate drug for treating tumors if it decreases expression of said one or more TEM genes.

66. The method of claim 66 wherein the cells are endothelial cells.

67. The method of claim 66 wherein the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs.

68. A method to identify candidate drugs for treating tumors, comprising:

contacting cells which express one or more TEM proteins selected from the group consisting of: 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 30, 31, 33, 35, 36, 37, 38, 39, 41,

42, 44, 45, and 46 as shown in SEQ ID NO: 198, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275, respectively, with a test compound;

determining amount of said one or more TEM proteins in said cells; and

identifying a test compound as a candidate drug for treating tumors if it decreases the amount of one more TEM proteins in said cells.

69. The method of claim 69 wherein the cells are endothelial cells.

70. The method of claim 69 wherein the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs.

71. A method to identify candidate drugs for treating tumors, comprising:

contacting cells which express one or more TEM proteins selected from the group consisting of: 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 198, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275 respectively, with a test compound;

determining activity of said one or more TEM proteins in said cells; and

identifying a test compound as a candidate drug for treating tumors if it decreases the activity of of one more TEM proteins in said cells.

72. The method of claim 72 wherein the cells are endothelial cells.

73. The method of claim 72 wherein the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs.

74. A method to identify candidate drugs for treating patients bearing tumors, comprising:

contacting a test compound with recombinant host cells which are transfected with an expression construct which encodes one or more TEM proteins selected from the group consisting of 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 198, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275, respectively;

determining proliferation of said cells; and

identifying a test compound which inhibits proliferation of said cells as a candidate drug for treating patients bearing tumors.

75. A method to identify candidate drugs for treating tumors, comprising:

contacting cells which express one or more NEM genes selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 278, 282, 284, and 288, respectively, with a test compound;

determining expression of said one or more NEM genes by hybridization of mRNA of said cells to a nucleic acid probe which is complementary to said mRNA; and

identifying a test compound as a candidate drug for treating tumors if it increases expression of said one or more NEM genes.

76. The method of claim 76 wherein the cells are endothelial cells.

77. The method of claim 76 wherein the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more NEMs.

78. A method to identify candidate drugs for treating tumors,

comprising:

contacting cells which express one or more NEM proteins
selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ
ID NO: 279, 283, 285, 286, 287, and 289, with a test compound;

determining amount of said one or more NEM proteins in
said cells; and

identifying a test compound as a candidate drug for
treating tumors if it increases the amount of one more NEM proteins in
said cells.

79. The method of claim 79 wherein the cells are endothelial cells.

80. The method of claim 79 wherein the cells are recombinant host
cells which are transfected with an expression construct which
encodes said one or more NEMs.

81. A method to identify candidate drugs for treating tumors, comprising:
- contacting cells which express one or more NEM proteins selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, with a test compound;
 - determining activity of said one or more NEM proteins in said cells; and
 - identifying a test compound as a candidate drug for treating tumors if it increases the activity of one more NEM proteins in said cells.
82. The method of claim 82 wherein the cells are endothelial cells.
83. The method of claim 82 wherein the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more NEMs.
84. A method to identify candidate drugs for treating patients bearing tumors, comprising:
- contacting a test compound with recombinant host cells which are transfected with an expression construct which encodes one or more NEM proteins selected from the group consisting of 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289;
 - determining proliferation of said cells; and
 - identifying a test compound which stimulates proliferation of said cells as a candidate drug for treating patients bearing tumors.
85. A method for identification of a ligand involved in endothelial cell regulation, comprising:
- contacting a test compound with a human transmembrane TEM protein selected from the group consisting of 1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 196,

198, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275;

determining binding of a test compound to the human transmembrane protein, wherein a test compound which binds to the protein is identified as a ligand involved in endothelial cell regulation.

86. A method of inducing an immune response in a mammal, comprising:
administering to the mammal a cell which expresses a transmembrane protein selected from the group consisting of: TEM 1, 9, 13, 17, 19, 22, 30, and 44 as shown in SEQ ID NO: 196, 212, 220, 230, 232, 238, 250 and 271, respectively, wherein the cell is a recombinant cell which comprises a vector encoding said transmembrane protein, or the cell is a fusion of a dendritic cell and a tumor endothelium cell, whereby an immune response to the human transmembrane protein is induced in the mammal.



Figure 1

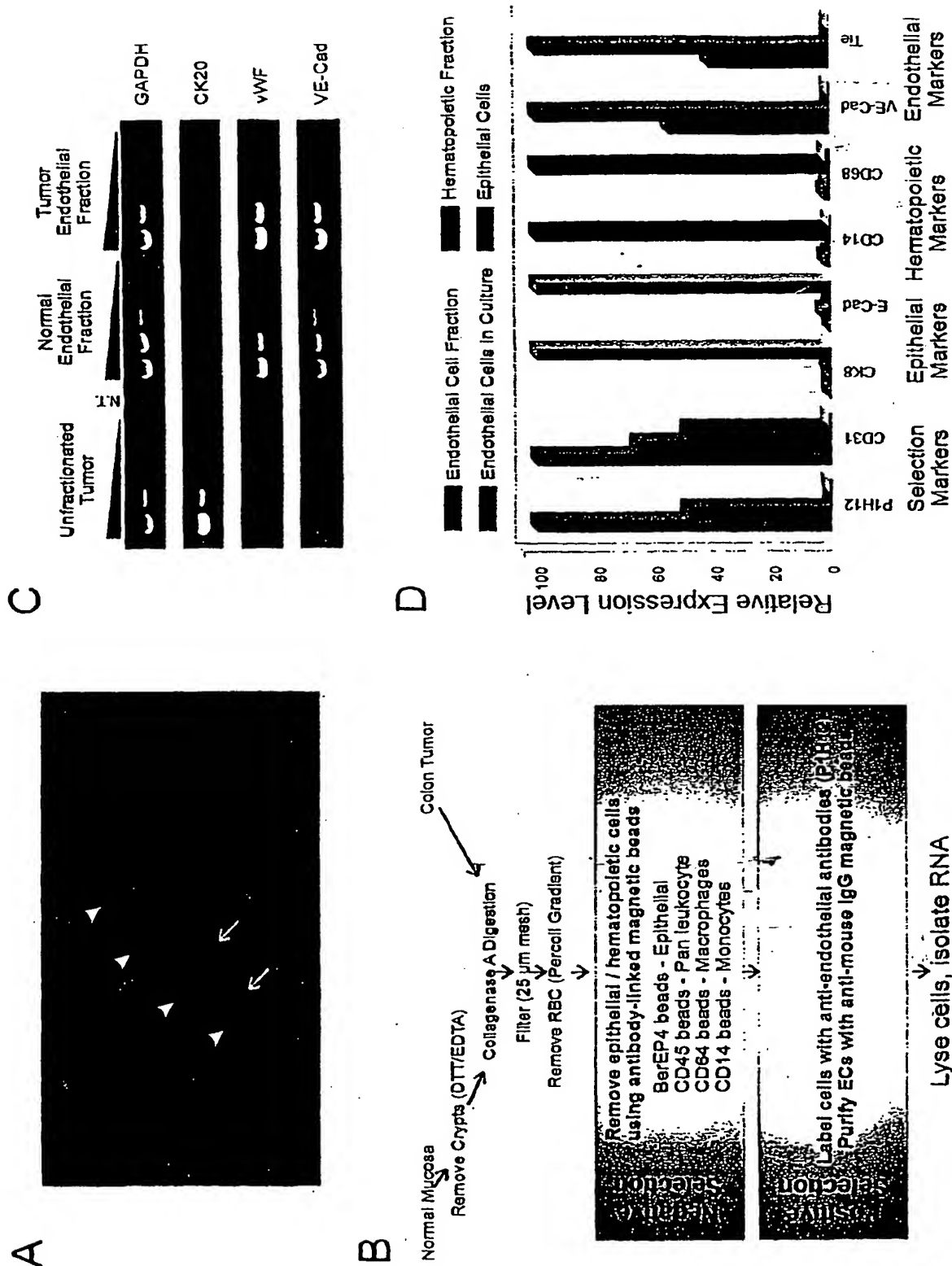


Figure 2

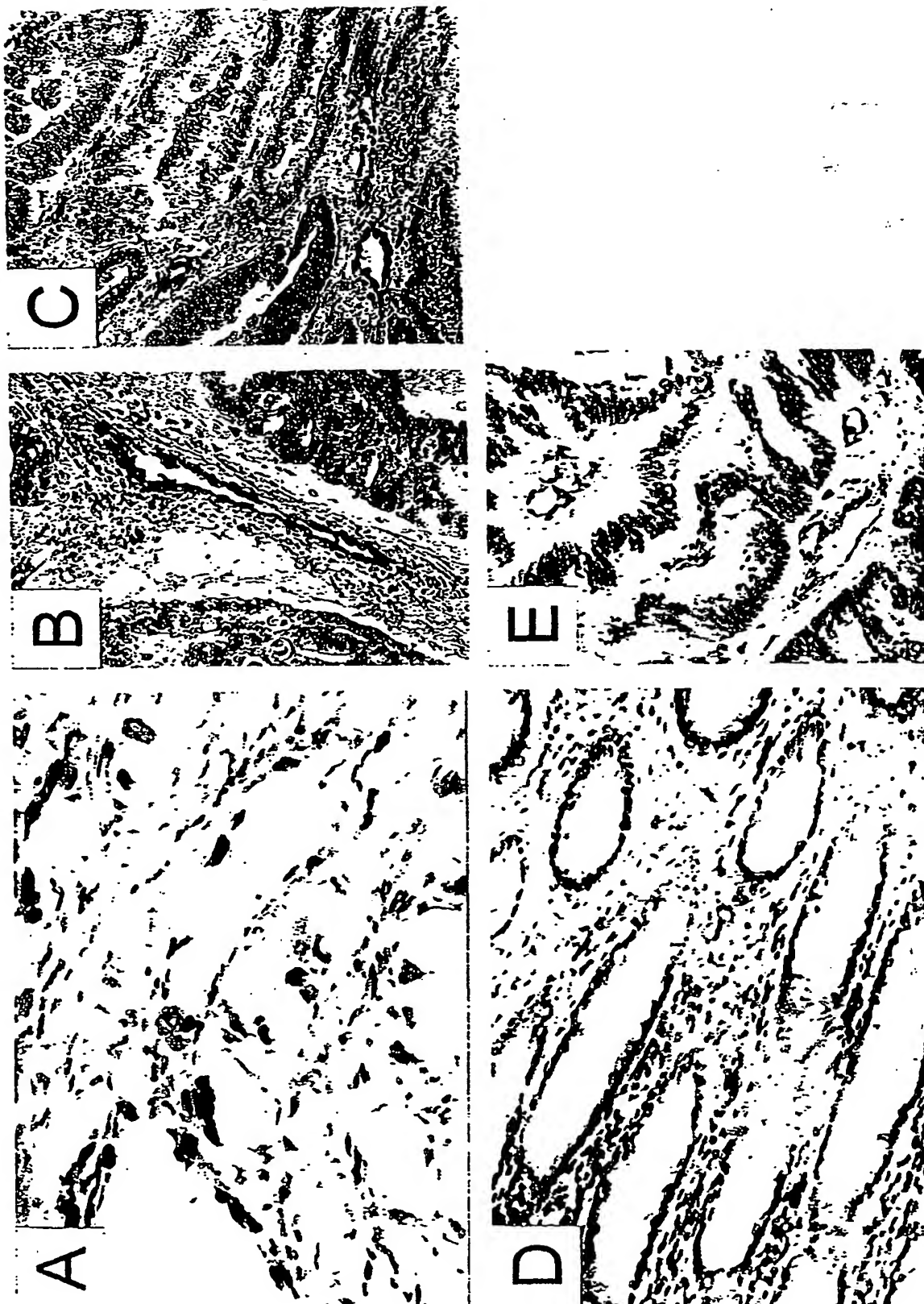


Figure 3

A

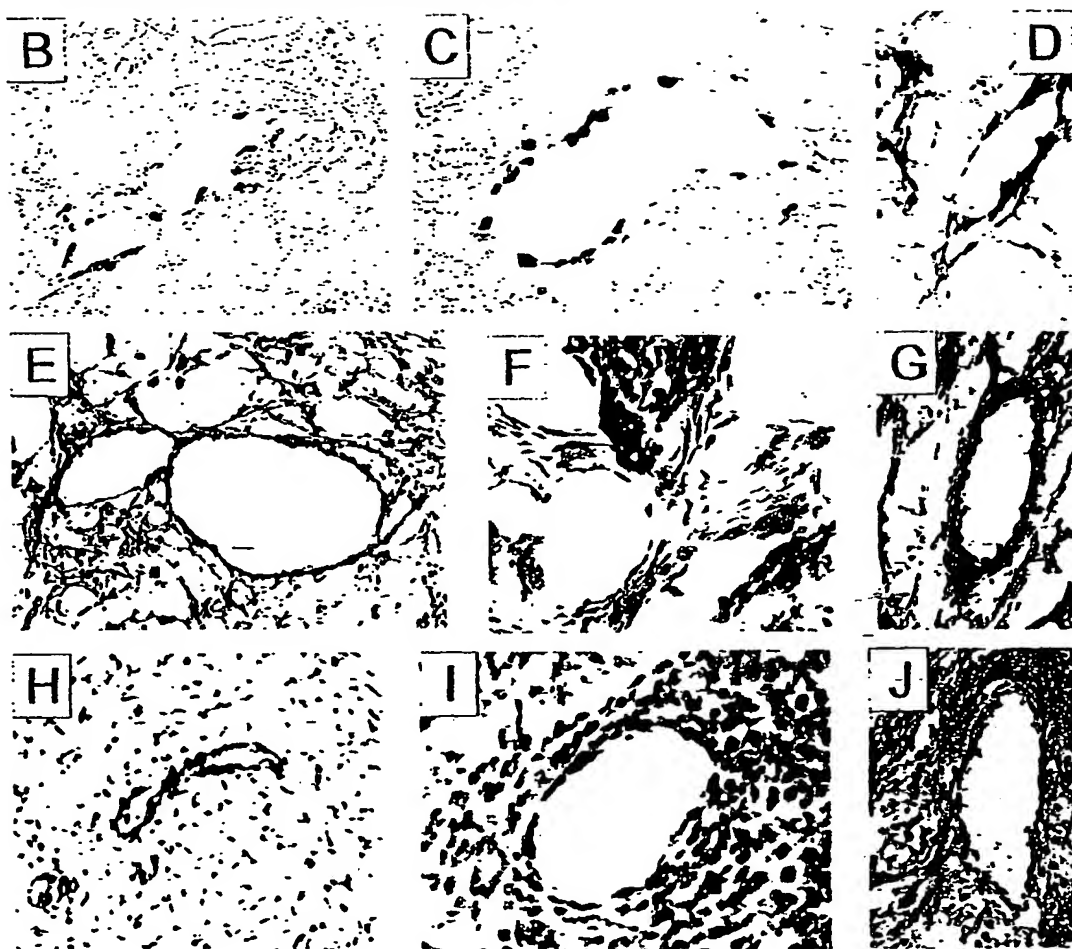
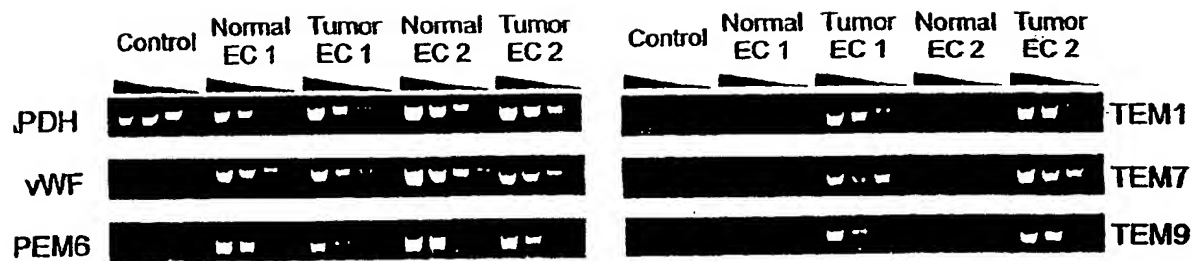


Figure 4

SEQUENCE LISTING

<110> Brad St. Croix
Bert Vogelstein
Kenneth Kinzler

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<212> DNA

<213> Homo sapiens

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<212> DNA

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Ala Phe Thr Asn Trp Ala Gln Pro Ala Ser Gly Gly Pro Cys Pro Ala
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Glu Gly Ala Cys Pro Ala Leu Gln Asp Glu Ala Gly Gln Ala Gly Pro
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Ala Val Tyr Thr Thr Pro Phe His Leu Val Ser Thr Glu Phe Glu Trp
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Leu Pro Phe Gly Ser Val Ala Ala Val Gln Cys Gln Ala Gly Arg Gly

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 Glu Asp Phe His Arg Lys Val Tyr Asn Ile Arg Gly Asp Met Tyr Gln
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Tyr Gly Pro Ser Glu Pro His Ser Arg Glu Leu Trp Val Asp Val Ala			
Glu Ala Asn Arg Ser Gln Val Lys Ile His Thr Ile Leu Ser Asn Thr			
His Arg Gln Ala Ser Arg Val Val Leu Ser Phe Asp Phe Pro Phe Tyr			
Gly His Pro Leu Arg Gln Ile Thr Ile Ala Thr Gly Gly Phe Ile Phe			
145 Met Gly Asp Val Ile His Arg Met Leu Thr Ala Thr Gln Tyr Val Ala			
Pro Leu Met Ala Asn Phe Asn Pro Gly Tyr Ser Asp Asn Ser Thr Val			
Val Tyr Phe Asp Asn Gly Thr Val Phe Val Val Gln Trp Asp His Val			
Tyr Leu Gln Gly Trp Glu Asp Lys Gly Ser Phe Thr Phe Gln Ala Ala			
Leu His His Asp Gly Arg Ile Val Phe Ala Tyr Lys Glu Ile Pro Met			
225 Ser Val Pro Glu Ile Ser Ser Ser Gln His Pro Val Lys Thr Gly Leu			
Ser Asp Ala Phe Met Ile Leu Asn Pro Ser Pro Asp Val Pro Glu Ser			
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Lys Val Thr Ser Met Ser Ala Val Glu Phe Thr Pro Leu Pro Thr Cys			
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Ile Asn Gly His Pro Thr Ser Asn Ala Ala Leu Phe Phe Ile Glu Arg			
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Ser Thr Tyr Ala Glu Val Glu Pro Ser Gly His Glu Lys Glu Gly Phe			

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 Tyr Tyr Val Ser Arg Leu Tyr Gly Pro Ser Glu Pro His Ser Arg Glu
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<210> 181

<211> 2157

<212> DNA

<213> Homo sapiens

<400> 181

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<210> 182

<211> 2535

<212> DNA

<213> Mus musculus

<400> 182

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<210> 183

<211> 5520

<212> DNA

<213> Mus musculus

<400> 183

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<211> 2833

<212> DNA

<213> Mus musculus

<400> 184

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<211> 2009

<212> DNA

<213> Mus musculus

<400> 185

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<212> DNA

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<211> 564
<212> PRT
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Phe Val Glu Gln Leu Ala His Lys Phe Ile Ser Pro Gln Leu Arg Met
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Ser Phe Ile Val Phe Ser Thr Arg Gly Thr Thr Leu Met Lys Leu Thr
85     90     95
Glu Asp Arg Glu Gln Ile Arg Gln Gly Leu Glu Glu Leu Gln Lys Val
100    105    110
Leu Pro Gly Gly Asp Thr Tyr Met His Glu Gly Phe Glu Arg Ala Ser
115    120    125
Glu Gln Ile Tyr Tyr Glu Asn Arg Gln Gly Tyr Arg Thr Ala Ser Val
130    135    140
Ile Ile Ala Leu Thr Asp Gly Glu Leu His Glu Asp Leu Phe Phe Tyr
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Ser Glu Arg Glu Ala Asn Arg Ser Arg Asp Leu Gly Ala Ile Val Tyr
165    170    175
Cys Val Gly Val Lys Asp Phe Asn Glu Thr Gln Leu Ala Arg Ile Ala
180    185    190
Asp Ser Lys Asp His Val Phe Pro Val Asn Asp Gly Phe Gln Ala Leu
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Gln Gly Ile Ile His Ser Ile Leu Lys Lys Ser Cys Ile Glu Ile Leu
210    215    220
Ala Ala Glu Pro Ser Thr Ile Cys Ala Gly Glu Ser Phe Gln Val Val
225    230    235    240
Val Arg Gly Asn Gly Phe Arg His Ala Arg Asn Val Asp Arg Val Leu
245    250    255
Cys Ser Phe Lys Ile Asn Asp Ser Val Thr Leu Asn Glu Lys Pro Phe
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Ser Val Glu Asp Thr Tyr Leu Leu Cys Pro Ala Pro Ile Leu Lys Glu
275    280    285
Val Gly Met Lys Ala Ala Leu Gln Val Ser Met Asn Asp Gly Leu Ser
290    295    300
Phe Ile Ser Ser Ser Val Ile Ile Thr Thr Thr His Cys Ser Asp Gly
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Ser Ile Leu Ala Ile Ala Leu Leu Ile Leu Phe Leu Leu Leu Ala Leu
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Ala Leu Leu Trp Trp Phe Trp Pro Leu Cys Cys Thr Val Ile Ile Lys
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Arg Val Lys Met Pro	Glu Gln Glu Tyr Glu	Phe Pro Glu Pro Arg Asn		
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Leu Asn Asn Asn Met	Arg Arg Pro Ser Ser	Pro Arg Lys Trp Tyr Ser		
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Pro Ile Lys Gly Lys	Leu Asp Ala Leu Trp	Val Leu Leu Arg Lys Gly		
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Tyr Asp Arg Val Ser	Val Met Arg Pro Gln	Pro Gly Asp Thr Gly Arg		
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Cys Ile Asn Phe Thr	Arg Val Lys Asn Asn	Gln Pro Ala Lys Tyr Pro		
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Thr Pro Pro Pro Pro	Ala Pro His Cys	Pro Pro Pro Pro Ser Ala		
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Pro Thr Pro Pro Ile	Pro Ser Pro Ser	Thr Leu Pro Pro Pro		
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<210> 188
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<400> 188
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Val Val Asp Leu Gly Thr Glu Phe Leu Thr Cys Asp Cys His Leu Arg
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Leu Gln Glu Ala Gln Leu Cys Cys Glu Gly Ala Leu Glu Leu His Thr

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Ala	Leu	Thr	Leu	Ala	His	Gln	Leu	Arg	Val	Tyr	Thr	Ala	Glu	Ala
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Ser	Phe	Ser	Asp	Met	Met	Asp	Val	Val	Tyr	Val	Ala	Gln	Met	Ile
	450				455				460					
Lys	Phe	Leu	Gly	Tyr	Val	Asp	Gln	Ile	Lys	Glu	Leu	Val	Glu	Val
465				470					475					480
Val	Asp	Met	Ala	Ser	Asn	Leu	Met	Leu	Val	Asp	Glu	His	Leu	Leu
			485					490					495	
Leu	Ala	Gln	Arg	Glu	Asp	Lys	Ala	Cys	Ser	Arg	Ile	Val	Gly	Ala
		500					505					510		
Glu	Arg	Ile	Gly	Gly	Ala	Ala	Leu	Ser	Pro	His	Ala	Gln	His	Ile
	515						520					525		
Val	Asn	Ala	Arg	Asn	Val	Ala	Leu	Glu	Ala	Tyr	Leu	Ile	Lys	Pro
	530				535					540				
Ser	Tyr	Val	Gly	Leu	Thr	Cys	Thr	Ala	Phe	Gln	Arg	Arg	Glu	Gly
545					550				555					560
Val	Pro	Gly	Thr	Arg	Pro	Gly	Ser	Pro	Gly	Gln	Asn	Pro	Pro	Pro
			565					570					575	
Pro	Glu	Pro	Pro	Ala	Asp	Gln	Gln	Leu	Arg	Phe	Arg	Cys	Thr	Thr
		580						585					590	
Arg	Pro	Asn	Val	Ser	Leu	Ser	Ser	Phe	His	Ile	Lys	Asn	Ser	Val
		595					600					605		
Leu	Ala	Ser	Ile	Gln	Leu	Pro	Pro	Ser	Leu	Phe	Ser	Ser	Leu	Pro
	610					615					620			
Ala	Leu	Ala	Pro	Pro	Val	Pro	Pro	Asp	Cys	Thr	Leu	Gln	Leu	Val
625					630					635				640
Phe	Arg	Asn	Gly	Arg	Leu	Phe	His	Ser	His	Ser	Asn	Thr	Ser	Arg
			645					650					655	
Gly	Ala	Ala	Gly	Pro	Gly	Lys	Arg	Arg	Gly	Val	Ala	Thr	Pro	Val
		660					665					670		
Phe	Ala	Gly	Thr	Ser	Gly	Cys	Gly	Val	Gly	Asn	Leu	Thr	Glu	Pro
	675						680				685			
Ala	Val	Ser	Leu	Arg	His	Trp	Ala	Glu	Gly	Ala	Glu	Pro	Val	Ala
	690					695					700			
Trp	Trp	Ser	Gln	Glu	Gly	Pro	Gly	Glu	Ala	Gly	Gly	Trp	Thr	Ser
705					710					715				720

Gly Cys Gln Leu Arg Ser Ser Gln Pro Asn Val Ser Ala Leu His Cys
 725 730 735
 Gln His Leu Gly Asn Val Ala Val Leu Met Glu Leu Ser Ala Phe Pro
 740 745 750
 Arg Glu Val Gly Gly Ala Gly Ala Gly Leu His Pro Val Val Tyr Pro
 755 760 765
 Cys Thr Ala Leu Leu Leu Leu Cys Leu Phe Ala Thr Ile Ile Thr Tyr
 770 775 780
 Ile Leu Asn His Ser Ser Ile Arg Val Ser Arg Lys Gly Trp His Met
 785 790 795 800
 Leu Leu Asn Leu Cys Phe His Ile Ala Met Thr Ser Ala Val Phe Ala
 805 810 815
 Gly Gly Ile Thr Leu Thr Asn Tyr Gln Met Val Cys Gln Ala Val Gly
 820 825 830
 Ile Thr Leu His Tyr Ser Ser Leu Ser Thr Leu Leu Trp Met Gly Val
 835 840 845
 Lys Ala Arg Val Leu His Lys Glu Leu Thr Trp Arg Ala Pro Pro Pro
 850 855 860
 Gln Glu Gly Asp Pro Ala Leu Pro Thr Pro Ser Pro Met Leu Arg Phe
 865 870 875 880
 Tyr Leu Ile Ala Gly Gly Ile Pro Leu Ile Ile Cys Gly Ile Thr Ala
 885 890 895
 Ala Val Asn Ile His Asn Tyr Arg Asp His Ser Pro Tyr Cys Trp Leu
 900 905 910
 Val Trp Arg Pro Ser Leu Gly Ala Phe Tyr Ile Pro Val Ala Leu Ile
 915 920 925
 Leu Leu Ile Thr Trp Ile Tyr Phe Leu Cys Ala Gly Leu Arg Leu Arg
 930 935 940
 Gly Pro Leu Ala Gln Asn Pro Lys Ala Gly Asn Ser Arg Ala Ser Leu
 945 950 955 960
 Glu Ala Gly Glu Glu Leu Arg Gly Ser Thr Arg Leu Arg Gly Ser Gly
 965 970 975
 Pro Leu Leu Ser Asp Ser Gly Ser Leu Leu Ala Thr Gly Ser Ala Arg
 980 985 990
 Val Gly Thr Pro Gly Pro Pro Glu Asp Gly Asp Ser Leu Tyr Ser Pro
 995 1000 1005
 Gly Val Gln Leu Gly Ala Leu Val Thr Thr His Phe Leu Tyr Leu Ala
 1010 1015 1020
 Met Trp Ala Cys Gly Ala Leu Ala Val Ser Gln Arg Trp Leu Pro Arg
 1025 1030 1035 1040
 Val Val Cys Ser Cys Leu Tyr Gly Val Ala Ala Ser Ala Leu Gly Leu
 1045 1050 1055
 Phe Val Phe Thr His His Cys Ala Arg Arg Arg Asp Val Arg Ala Ser
 1060 1065 1070
 Trp Arg Ala Cys Cys Pro Pro Ala Ser Pro Ala Ala Pro His Ala Pro
 1075 1080 1085
 Pro Arg Ala Leu Pro Ala Ala Ala Glu Asp Gly Ser Pro Val Phe Gly
 1090 1095 1100
 Glu Gly Pro Pro Ser Leu Lys Ser Ser Pro Ser Gly Ser Ser Gly His
 1105 1110 1115 1120
 Pro Leu Ala Leu Gly Pro Cys Lys Leu Thr Asn Leu Gln Leu Ala Gln
 1125 1130 1135
 Ser Gln Val Cys Glu Ala Gly Ala Ala Ala Gly Gly Glu Gly Glu Pro
 1140 1145 1150
 Glu Pro Ala Gly Thr Arg Gly Asn Leu Ala His Arg His Pro Asn Asn
 1155 1160 1165
 Val His His Gly Arg Arg Ala His Lys Ser Arg Ala Lys Gly His Arg
 1170 1175 1180
 Ala Gly Glu Ala Cys Gly Lys Asn Arg Leu Lys Ala Leu Arg Gly Gly
 1185 1190 1195 1200
 Ala Ala Gly Ala Leu Glu Leu Leu Ser Ser Glu Ser Gly Ser Leu His

1205								1210				1215			
Asn	Ser	Pro	Thr	Asp	Ser	Tyr	Leu	Gly	Ser	Ser	Arg	Asn	Ser	Pro	Gly
1220								1225				1230			
Ala	Gly	Leu	Gln	Leu	Glu	Gly	Glu	Pro	Met	Leu	Thr	Pro	Ser	Glu	Gly
1235								1240				1245			
Ser	Asp	Thr	Ser	Ala	Ala	Pro	Leu	Ser	Glu	Ala	Gly	Arg	Ala	Gly	Gln
1250								1255				1260			
Arg	Arg	Ser	Ala	Ser	Arg	Asp	Ser	Leu	Lys	Gly	Gly	Gly	Ala	Leu	Glu
1265								1270				1275			
Lys	Glu	Ser	His	Arg	Arg	Ser	Tyr	Pro	Leu	Asn	Ala	Ala	Ser	Leu	Asn
1285								1290				1295			
Gly	Ala	Pro	Lys	Gly	Gly	Lys	Tyr	Asp	Asp	Val	Thr	Leu	Met	Gly	Ala
1300								1305				1310			
Glu	Val	Ala	Ser	Gly	Gly	Cys	Met	Lys	Thr	Gly	Leu	Trp	Lys	Ser	Glu
1315								1320				1325			
Thr	Thr	Val													
1330															

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<210> 189
<211> 529
<212> PRT
<213> Homo sapiens
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<400> 189															
Met 1	Ala	Arg	Phe 5	Pro	Lys	Ala	Asp	Leu 10	Ala	Ala	Ala	Gly	Val 15	Met	Leu
Leu	Cys	His	Phe 20	Thr	Asp	Gln	Phe 25	Gln	Phe	Ala	Asp	Gly 30	Lys	Pro	
Gly	Asp	Gln 35	Ile	Leu	Asp	Trp 40	Gln	Tyr	Gly	Val	Thr	Gln 45	Ala	Phe	Pro
His	Thr 50	Glu	Glu	Glu	Val	Glu 55	Val	Asp	Ser	His 60	Tyr	Ser	His	Arg	
Trp 65	Lys	Arg	Asn	Leu	Asp 70	Phe	Leu	Lys	Ala 75	Val	Asp	Thr	Asn	Arg	Ala 80
Ser	Val	Gly	Gln	Asp 85	Ser	Pro	Glu	Pro	Arg 90	Ser	Phe	Thr	Asp	Leu 95	Leu
Leu	Asp	Asp	Gly 100	Gln	Asp	Asn	Asn	Thr 105	Gln	Ile	Glu	Glu	Asp	Thr	Asp
His	Asn 115	Tyr	Tyr	Ile	Ser	Arg	Ile 120	Tyr	Gly	Pro	Ser	Asp 125	Ser	Ala	Ser
Arg	Asp 130	Leu	Trp	Val	Asn 135	Ile	Asp	Gln	Met	Glu	Lys 140	Asp	Lys	Val	Lys
Ile 145	His	Gly	Ile	Leu	Ser 150	Asn	Thr	His	Arg	Gln 155	Ala	Ala	Arg	Val	Asn 160
Leu	Ser	Phe	Asp 165	Pro	Phe	Tyr	Gly	His 170	Phe	Leu	Arg	Glu	Ile 175	Thr	
Val	Ala	Thr 180	Gly	Gly	Phe	Ile	Tyr	Thr 185	Gly	Glu	Val	Val	His 190	Arg	Met
Leu	Thr 195	Ala	Thr	Gln	Tyr	Ile	Ala 200	Pro	Leu	Met	Ala	Asn 205	Phe	Asp	Pro
Ser	Val 210	Ser	Arg	Asn	Ser	Thr 215	Val	Arg	Tyr	Phe	Asp 220	Asn	Gly	Thr	Ala
Leu 225	Val	Val	Gln	Trp	Asp 230	His	Val	His	Leu	Gln 235	Asp	Asn	Tyr	Asn	Leu 240
Gly	Ser	Phe	Thr 245	Phe	Gln	Ala	Thr	Leu	Leu	Met 250	Asp	Gly	Arg	Ile 255	Ile
Phe	Gly	Tyr 260	Lys	Glu	Ile	Pro	Val	Leu 265	Val	Thr	Gln	Ile	Ser 270	Ser	Thr
Asn	His 275	Pro	Val	Lys	Val	Gly	Leu 280	Ser	Asp	Ala	Phe	Val	Val	Val	His
Arg	Ile	Gln	Gln	Ile	Pro	Asn	Val	Arg	Arg	Arg	Thr	Ile	Tyr	Glu	Tyr

290 295 300
 His Arg Val Glu Leu Gln Met Ser Lys Ile Thr Asn Ile Ser Ala Val
 305 310 315 320
 Glu Met Thr Pro Leu Pro Thr Cys Leu Gln Phe Asn Arg Cys Gly Pro
 325 330 335
 Cys Val Ser Ser Gln Ile Gly Phe Asn Cys Ser Trp Cys Ser Lys Leu
 340 345 350
 Gln Arg Cys Ser Ser Gly Phe Asp Arg His Arg Gln Asp Trp Val Asp
 355 360 365
 Ser Gly Cys Pro Glu Glu Ser Lys Glu Lys Met Cys Glu Asn Thr Glu
 370 375 380
 Pro Val Glu Thr Ser Ser Arg Thr Thr Thr Thr Ile Gly Ala Thr Thr
 385 390 395 400
 Thr Gln Phe Arg Val Leu Thr Thr Thr Arg Arg Ala Val Thr Ser Gln
 405 410 415
 Phe Pro Thr Ser Leu Pro Thr Glu Asp Asp Thr Lys Ile Ala Leu His
 420 425 430
 Leu Lys Asp Asn Gly Ala Ser Thr Asp Asp Ser Ala Ala Glu Lys Lys
 435 440 445
 Gly Gly Thr Leu His Ala Gly Leu Ile Val Gly Ile Leu Ile Leu Val
 450 455 460
 Leu Ile Val Ala Thr Ala Ile Leu Val Thr Val Tyr Met Tyr His His
 465 470 475 480
 Pro Thr Ser Ala Ala Ser Ile Phe Phe Ile Glu Arg Arg Pro Ser Arg
 485 490 495
 Trp Pro Ala Met Lys Phe Arg Arg Gly Ser Gly His Pro Ala Tyr Ala
 500 505 510
 Glu Val Glu Pro Val Gly Glu Lys Glu Gly Phe Ile Val Ser Glu Gln
 515 520 525
 Cys

<210> 190
 <211> 765
 <212> PRT
 <213> Mus musculus

<400> 190
 Met Leu Leu Arg Leu Leu Leu Ala Trp Val Ala Ala Val Pro Ala Leu
 1 5 10 15
 Gly Gln Val Pro Thr Pro Glu Pro Arg Ala Ala Cys Gly Pro Ser
 20 25 30
 Ser Cys Tyr Ala Leu Phe Pro Arg Arg Arg Thr Phe Leu Glu Ala Trp
 35 40 45
 Arg Ala Cys Arg Glu Leu Gly Gly Asn Leu Ala Thr Pro Arg Thr Pro
 50 55 60
 Glu Glu Ala Gln Arg Val Asp Ser Leu Val Gly Val Gly Pro Ala Asn
 65 70 75 80
 Gly Leu Leu Trp Ile Gly Leu Gln Arg Gln Ala Arg Gln Cys Gln Pro
 85 90 95
 Gln Arg Pro Leu Arg Gly Phe Ile Trp Thr Thr Gly Asp Gln Asp Thr
 100 105 110
 Ala Phe Thr Asn Trp Ala Gln Pro Ala Thr Glu Gly Pro Cys Pro Ala
 115 120 125
 Gln Arg Cys Ala Ala Leu Glu Ala Ser Gly Glu His Arg Trp Leu Glu
 130 135 140
 Gly Ser Cys Thr Leu Ala Val Asp Gly Tyr Leu Cys Gln Phe Gly Phe
 145 150 155 160
 Glu Gly Ala Cys Pro Ala Leu Pro Leu Glu Val Gly Gln Ala Gly Pro
 165 170 175
 Ala Val Tyr Thr Thr Pro Phe Asn Leu Val Ser Ser Glu Phe Glu Trp

48

Thr Ala Ala Pro Thr Ala Leu Ala Glu Ser Gly Leu Ala Gly Gln Ser
 675 680 685
 Gln Arg Asp Asp Arg Trp Leu Leu Val Ala Leu Leu Val Pro Thr Cys
 690 695 700
 Val Phe Leu Val Val Leu Leu Ala Leu Gly Ile Val Tyr Cys Thr Arg
 705 710 715 720
 Cys Gly Ser His Ala Pro Asn Lys Arg Ile Thr Asp Cys Tyr Arg Trp
 725 730 735
 Val Thr His Ala Gly Asn Lys Ser Ser Thr Glu Pro Met Pro Pro Arg
 740 745 750
 Gly Ser Leu Thr Gly Val Gln Thr Cys Arg Thr Ser Val
 755 760 765

<210> 191
 <211> 1329
 <212> PRT
 <213> Mus musculus

<400> 191
 Met Pro Val Pro Pro Ala Arg Leu Leu Leu Leu Pro Leu Leu Pro Cys
 1 5 10 15
 Leu Leu Leu Leu Ala Pro Gly Thr Arg Gly Ala Pro Gly Cys Pro Val
 20 25 30
 Pro Ile Arg Gly Cys Lys Cys Ser Gly Glu Arg Pro Lys Gly Leu Ser
 35 40 45
 Gly Gly Ala His Asn Pro Ala Arg Arg Arg Val Val Cys Gly Gly Gly
 50 55 60
 Asp Leu Pro Glu Pro Pro Asp Pro Gly Leu Leu Pro Asn Gly Thr Ile
 65 70 75 80
 Thr Leu Leu Leu Ser Asn Asn Lys Ile Thr Gly Leu Arg Asn Gly Ser
 85 90 95
 Phe Leu Gly Leu Ser Leu Leu Glu Lys Leu Asp Leu Arg Ser Asn Val
 100 105 110
 Ile Ser Thr Val Gln Pro Gly Ala Phe Leu Gly Leu Gly Glu Leu Lys
 115 120 125
 Arg Leu Asp Leu Ser Asn Asn Arg Ile Gly Cys Leu Thr Ser Glu Thr
 130 135 140
 Phe Gln Gly Leu Pro Arg Leu Leu Arg Leu Asn Ile Ser Gly Asn Ile
 145 150 155 160
 Tyr Ser Ser Leu Gln Pro Gly Val Phe Asp Glu Leu Pro Ala Leu Lys
 165 170 175
 Ile Val Asp Phe Gly Thr Glu Phe Leu Thr Cys Asp Cys Arg Leu Arg
 180 185 190
 Trp Leu Leu Pro Trp Ala Arg Asn His Ser Leu Gln Leu Ser Glu Arg
 195 200 205
 Thr Leu Cys Ala Tyr Pro Ser Ala Leu His Ala His Ala Leu Ser Ser
 210 215 220
 Leu Gln Glu Ser Gln Leu Arg Cys Glu Gly Ala Leu Glu Leu His Thr
 225 230 235 240
 His Tyr Leu Ile Pro Ser Leu Arg Gln Val Phe Gln Gly Asp Arg
 245 250 255
 Leu Pro Phe Gln Cys Ser Ala Ser Tyr Leu Gly Asn Asp Thr Arg Ile
 260 265 270
 His Trp Tyr His Asn Gly Ala Pro Met Glu Ser Asp Glu Gln Ala Gly
 275 280 285
 Ile Val Leu Ala Glu Asn Leu Ile His Asp Cys Thr Phe Ile Thr Ser
 290 295 300
 Glu Leu Thr Leu Ser His Ile Gly Val Trp Ala Ser Gly Glu Trp Glu
 305 310 315 320
 Cys Ser Val Ser Thr Val Gln Gly Asn Thr Ser Lys Lys Val Glu Ile
 325 330 335

Val Val Leu Glu Thr Ser Ala Ser Tyr Cys Pro Ala Glu Arg Val Thr
 340 345 350
 Asn Asn Arg Gly Asp Phe Arg Trp Pro Arg Thr Leu Ala Gly Ile Thr
 355 360 365
 Ala Tyr Gln Ser Cys Leu Gln Tyr Pro Phe Thr Ser Val Pro Leu Ser
 370 375 380
 Gly Gly Ala Pro Gly Thr Arg Ala Ser Arg Arg Cys Asp Arg Ala Gly
 385 390 395 400
 Arg Trp Glu Pro Gly Asp Tyr Ser His Cys Leu Tyr Thr Asn Asp Ile
 405 410 415
 Thr Arg Val Leu Tyr Thr Phe Val Leu Met Pro Ile Asn Ala Ser Asn
 420 425 430
 Ala Leu Thr Leu Ala His Gln Leu Arg Val Tyr Thr Ala Glu Ala Ala
 435 440 445
 Ser Phe Ser Asp Met Met Asp Val Val Tyr Val Ala Gln Met Ile Gln
 450 455 460
 Lys Phe Leu Gly Tyr Val Asp Gln Ile Lys Glu Leu Val Glu Val Met
 465 470 475 480
 Val Asp Met Ala Ser Asn Leu Met Leu Val Asp Glu His Leu Leu Trp
 485 490 495
 Leu Ala Gln Arg Glu Asp Lys Ala Cys Ser Gly Ile Val Gly Ala Leu
 500 505 510
 Glu Arg Ile Gly Gly Ala Ala Leu Ser Pro His Ala Gln His Ile Ser
 515 520 525
 Val Asn Ser Arg Asn Val Ala Leu Glu Ala Tyr Leu Ile Lys Pro His
 530 535 540
 Ser Tyr Val Gly Leu Thr Cys Thr Ala Phe Gln Arg Arg Glu Val Gly
 545 550 555 560
 Val Ser Gly Ala Gln Pro Ser Ser Val Gly Gln Asp Ala Pro Val Glu
 565 570 575
 Pro Glu Pro Leu Ala Asp Gln Gln Leu Arg Phe Arg Cys Thr Thr Gly
 580 585 590
 Arg Pro Asn Ile Ser Leu Ser Ser Phe His Ile Lys Asn Ser Val Ala
 595 600 605
 Leu Ala Ser Ile Gln Leu Pro Pro Ser Leu Phe Ser Thr Leu Pro Ala
 610 615 620
 Ala Leu Ala Pro Pro Val Pro Pro Asp Cys Thr Leu Gln Leu Leu Val
 625 630 635 640
 Phe Arg Asn Gly Arg Leu Phe Arg Ser His Gly Asn Asn Thr Ser Arg
 645 650 655
 Pro Gly Ala Ala Gly Pro Gly Lys Arg Arg Gly Val Ala Thr Pro Val
 660 665 670
 Ile Phe Ala Gly Thr Ser Gly Cys Gly Val Gly Asn Leu Thr Glu Pro
 675 680 685
 Val Ala Val Ser Leu Arg His Trp Ala Glu Gly Ala Asp Pro Met Ala
 690 695 700
 Ala Trp Trp Asn Gln Asp Gly Pro Gly Gly Trp Ser Ser Glu Gly Cys
 705 710 715 720
 Arg Leu Arg Tyr Ser Gln Pro Asn Val Ser Ser Leu Tyr Cys Gln His
 725 730 735
 Leu Gly Asn Val Ala Val Leu Met Glu Leu Asn Ala Phe Pro Arg Glu
 740 745 750
 Ala Gly Gly Ser Gly Ala Gly Leu His Pro Val Val Tyr Pro Cys Thr
 755 760 765
 Ala Leu Leu Leu Cys Leu Phe Ser Thr Ile Ile Thr Tyr Ile Leu
 770 775 780
 Asn His Ser Ser Ile His Val Ser Arg Lys Gly Trp His Met Leu Leu
 785 790 795 800
 Asn Leu Cys Phe His Met Ala Met Thr Ser Ala Val Phe Val Gly Gly
 805 810 815
 Val Thr Leu Thr Asn Tyr Gln Met Val Cys Gln Ala Val Gly Ile Thr

51

Ile Ala Gly Gly Ser Met Lys Thr Gly Leu Trp Lys Ser Glu Thr Thr
 1315 1320 1325
 Val

<210> 192
 <211> 500
 <212> PRT
 <213> Mus musculus

<400> 192
 Met Arg Ala Gln Leu Trp Leu Leu Gln Leu Leu Leu Leu Arg Gly Ala
 1 5 10 15
 Ala Arg Ala Leu Ser Pro Ala Thr Pro Ala Gly His Asn Glu Gly Gln
 20 25 30
 Asp Ser Ala Trp Thr Ala Lys Arg Thr Arg Gln Gly Trp Ser Arg Arg
 35 40 45
 Pro Arg Glu Ser Pro Ala Gln Val Leu Lys Pro Gly Lys Thr Gln Leu
 50 55 60
 Ser Gln Asp Leu Gly Gly Gly Ser Leu Ala Ile Asp Thr Leu Pro Asp
 65 70 75 80
 Asn Arg Thr Arg Val Glu Asp Asn His Asn Tyr Tyr Val Ser Arg
 85 90 95
 Val Tyr Gly Pro Gly Glu Lys Gln Ser Gln Asp Leu Trp Val Asp Leu
 100 105 110
 Ala Val Ala Asn Arg Ser His Val Lys Ile His Arg Ile Leu Ser Ser
 115 120 125
 Ser His Arg Gln Ala Ser Arg Val Val Leu Ser Phe Asp Phe Pro Phe
 130 135 140
 Tyr Gly His Pro Leu Arg Gln Ile Thr Ile Ala Thr Gly Gly Phe Ile
 145 150 155 160
 Phe Met Gly Asp Met Leu His Arg Met Leu Thr Ala Thr Gln Tyr Val
 165 170 175
 Ala Pro Leu Met Ala Asn Phe Asn Pro Gly Tyr Ser Asp Asn Ser Thr
 180 185 190
 Val Ala Tyr Phe Asp Asn Gly Thr Val Phe Val Val Gln Trp Asp His
 195 200 205
 Val Tyr Leu Gln Asp Arg Glu Asp Arg Gly Ser Phe Thr Phe Gln Ala
 210 215 220
 Ala Leu His Arg Asp Gly Arg Ile Val Phe Gly Tyr Lys Glu Ile Pro
 225 230 235 240
 Met Ala Val Leu Asp Ile Ser Ser Ala Gln His Pro Val Lys Ala Gly
 245 250 255
 Leu Ser Asp Ala Phe Met Ile Leu Asn Ser Ser Pro Glu Val Pro Glu
 260 265 270
 Ser Gln Arg Arg Thr Ile Phe Glu Tyr His Arg Val Glu Leu Asp Ser
 275 280 285
 Ser Lys Ile Thr Thr Thr Ser Ala Val Glu Phe Thr Pro Leu Pro Thr
 290 295 300
 Cys Leu Gln His Gln Ser Cys Asp Thr Cys Val Ser Ser Asn Leu Thr
 305 310 315 320
 Phe Asn Cys Ser Trp Cys His Val Leu Gln Arg Cys Ser Ser Gly Phe
 325 330 335
 Asp Arg Tyr Arg Gln Glu Trp Leu Thr Tyr Gly Cys Ala Gln Glu Ala
 340 345 350
 Glu Gly Lys Thr Cys Glu Asp Phe Gln Asp Asp Ser His Tyr Ser Ala
 355 360 365
 Ser Pro Asp Ser Ser Phe Ser Pro Phe Asn Gly Asp Ser Thr Thr Ser
 370 375 380
 Ser Ser Leu Phe Ile Asp Ser Leu Thr Thr Glu Asp Asp Thr Lys Leu
 385 390 395 400

Asn Pro Tyr Ala Glu Gly Asp Gly Leu Pro Asp His Ser Ser Pro Lys
 405 410 415
 Ser Lys Gly Pro Pro Val His Leu Gly Thr Ile Val Gly Ile Val Leu
 420 425 430
 Ala Val Leu Leu Val Ala Ala Ile Ile Leu Ala Gly Ile Tyr Ile Ser
 435 440 445
 Gly His Pro Asn Ser Asn Ala Ala Leu Phe Phe Ile Glu Arg Arg Pro
 450 455 460
 His His Trp Pro Ala Met Lys Phe His Asn His Pro Asn His Ser Thr
 465 470 475 480
 Tyr Thr Glu Val Glu Pro Ser Gly His Glu Lys Glu Gly Phe Val Glu
 485 490 495
 Ala Glu Gln Cys
 500

<210> 193
 <211> 530
 <212> PRT
 <213> Mus musculus

<400> 193
 Met Ala Arg Phe Arg Arg Ala Asp Leu Ala Ala Gly Val Met Leu
 1 5 10 15
 Leu Cys His Phe Leu Thr Asp Arg Phe His Phe Ala His Gly Glu Pro
 20 25 30
 Gly His His Thr Asn Asp Trp Ile Tyr Glu Val Thr Asn Ala Phe Pro
 35 40 45
 Trp Asn Glu Glu Gly Val Glu Val Asp Ser Gln Ala Tyr Asn His Arg
 50 55 60
 Trp Lys Arg Asn Val Asp Pro Phe Lys Ala Val Asp Thr Asn Arg Ala
 65 70 75 80
 Ser Met Gly Gln Ala Ser Pro Glu Ser Lys Gly Phe Thr Asp Leu Leu
 85 90 95
 Leu Asp Asp Gly Gln Asp Asn Asn Thr Gln Ile Glu Glu Asp Thr Asp
 100 105 110
 His Asn Tyr Thr Ile Ser Arg Ile Tyr Gly Pro Ala Asp Ser Ala Ser
 115 120 125
 Arg Asp Leu Trp Val Asn Ile Asp Gln Met Glu Lys Asp Lys Val Lys
 130 135 140
 Ile His Gly Ile Leu Ser Asn Thr His Arg Gln Ala Ala Arg Val Asn
 145 150 155 160
 Leu Ser Phe Asp Phe Pro Phe Tyr Gly His Phe Leu Asn Glu Val Thr
 165 170 175
 Val Ala Thr Gly Gly Phe Ile Tyr Thr Gly Glu Val Val His Arg Met
 180 185 190
 Leu Thr Ala Thr Gln Tyr Ile Ala Pro Leu Met Ala Asn Phe Asp Pro
 195 200 205
 Ser Val Ser Arg Asn Ser Thr Val Arg Tyr Phe Asp Asn Gly Thr Ala
 210 215 220
 Leu Val Val Gln Trp Asp His Val His Leu Gln Asp Asn Tyr Asn Leu
 225 230 235 240
 Gly Ser Phe Thr Phe Gln Ala Thr Leu Leu Met Asp Gly Arg Ile Ile
 245 250 255
 Phe Gly Tyr Lys Glu Ile Pro Val Leu Val Thr Gln Ile Ser Ser Thr
 260 265 270
 Asn His Pro Val Lys Val Gly Leu Ser Asp Ala Phe Val Val Val His
 275 280 285
 Arg Ile Gln Gln Ile Pro Asn Val Arg Arg Arg Thr Ile Tyr Glu Tyr
 290 295 300
 His Arg Val Glu Leu Gln Met Ser Lys Ile Thr Asn Ile Ser Ala Val
 305 310 315 320

[illegible]

<210> 194
<211> 562
<212> PRT
<213> Mus musculus

<400> 194															
Met 1	Asp	Arg	Ala	Gly 5	Arg	Leu	Gly	Ala	Gly 10	Leu	Arg	Gly	Leu	Cys 15	Val
Ala	Ala	Leu	Val	Leu 20	Val	Cys	Ala	Gly 25	His	Gly	Gly	Arg	Arg	Glu 30	Asp
Gly	Gly	Pro	Ala	Cys 35	Tyr	Gly	Gly 40	Phe	Asp	Leu	Tyr	Phe	Ile	Leu 45	Asp
Lys	Ser	Gly	Ser	Val	Leu	His	His 55	Trp	Asn	Glu	Ile	Tyr	Tyr	Phe 60	Val
Glu 65	Gln	Leu	Ala	His	Arg	Phe	Ile 70	Ser	Pro	Gln	Leu	Arg	Met	Ser 80	Phe
Ile	Val	Phe	Ser	Thr 85	Arg	Gly	Thr	Thr	Leu	Met	Lys	Leu	Thr	Glu 95	Asp
Arg	Glu	Gln	Ile	Arg 100	Gln	Gly	Leu	Glu	Glu	Leu	Gln	Lys	Val	Leu 110	Pro
Gly	Gly	Asp	Thr	Tyr 115	Met	His	Glu	Gly	Phe	Glu	Arg	Ala	Ser	Glu 125	Gln
Ile	Tyr	Tyr	Glu	Asn 130	Ser	Gln	Gly	Tyr	Arg	Thr	Ala	Ser	Val	Ile 140	Ile
Ala 145	Leu	Thr	Asp	Gly	Glu	Leu	His	Glu	Asp	Leu	Phe	Phe	Tyr	Ser 160	Glu
Arg	Glu	Ala	Asn	Arg 165	Ser	Arg	Asp	Leu	Gly	Ala	Ile	Val	Tyr	Cys 175	Val
Gly	Val	Lys	Asp	Phe 180	Asn	Glu	Thr	Gln	Leu	Ala	Arg	Ile	Ala	Asp 190	Ser
Lys	Asp	His	Val	Phe 195	Pro	Val	Asn	Asp	Gly	Phe	Gln	Ala	Leu	Gln 205	Gly

Ile Ile His Ser Ile Leu Lys Lys Ser Cys Ile Glu Ile Leu Ala Ala
 210 215 220
 Glu Pro Ser Thr Ile Cys Ala Gly Glu Ser Phe Gln Val Val Val Arg
 225 230 235 240
 Gly Asn Gly Phe Arg His Ala Arg Asn Val Asp Arg Val Leu Cys Ser
 245 250 255
 Phe Lys Ile Asn Asp Ser Val Thr Leu Asn Glu Lys Pro Phe Ala Val
 260 265 270
 Glu Asp Thr Tyr Leu Leu Cys Pro Ala Pro Ile Leu Lys Glu Val Gly
 275 280 285
 Met Lys Ala Ala Leu Gln Val Ser Met Asn Asp Gly Leu Ser Phe Ile
 290 295 300
 Ser Ser Ser Val Ile Ile Thr Thr Thr His Cys Ser Asp Gly Ser Ile
 305 310 315 320
 Leu Ala Ile Ala Leu Leu Val Leu Phe Leu Leu Leu Ala Leu Ala Leu
 325 330 335
 Leu Trp Trp Phe Trp Pro Leu Cys Cys Thr Val Ile Ile Lys Glu Val
 340 345 350
 Pro Pro Pro Pro Val Glu Glu Ser Glu Glu Glu Asp Asp Gly Leu
 355 360 365
 Pro Lys Lys Lys Trp Pro Thr Val Asp Ala Ser Tyr Tyr Gly Gly Arg
 370 375 380
 Gly Val Gly Gly Ile Lys Arg Met Glu Val Arg Trp Gly Glu Lys Gly
 385 390 395 400
 Ser Thr Glu Glu Gly Ala Lys Leu Glu Lys Ala Lys Asn Ala Arg Val
 405 410 415
 Lys Met Pro Glu Gln Glu Tyr Glu Phe Pro Glu Pro Arg Asn Leu Asn
 420 425 430
 Asn Asn Met Arg Arg Pro Ser Ser Pro Arg Lys Trp Tyr Ser Pro Ile
 435 440 445
 Lys Gly Lys Leu Asp Ala Leu Trp Val Leu Leu Arg Lys Gly Tyr Asp
 450 455 460
 Arg Val Ser Val Met Arg Pro Gln Pro Gly Asp Thr Gly Arg Cys Ile
 465 470 475 480
 Asn Phe Thr Arg Val Lys Asn Ser Gln Pro Ala Lys Tyr Pro Leu Asn
 485 490 495
 Asn Thr Tyr His Pro Ser Ser Pro Pro Ala Pro Ile Tyr Thr Pro
 500 505 510
 Pro Pro Pro Ala Pro His Cys Pro Pro Pro Ala Pro Ser Ala Pro Thr
 515 520 525
 Pro Pro Ile Pro Ser Pro Pro Thr Leu Pro Pro Pro Gln Ala
 530 535 540
 Pro Pro Pro Asn Arg Ala Pro Pro Pro Ser Arg Pro Pro Pro Arg Pro
 545 550 555 560
 Ser Val

<210> 195

<211> 2565

<212> DNA

<213> Homo sapiens

<400> 195

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<210> 196

<211> 757

<212> PRT

<213> Homo sapiens

<400> 196

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50     55     60
Glu Glu Ala Gln Arg Val Asp Ser Leu Val Gly Ala Gly Pro Ala Ser
65     70     75     80
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Lys Ala Pro Gln Ile Pro Arg Glu Asp Gly Pro Ser Pro Lys Leu Ala
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 660 665 670
 Glu Ala Gly Leu Ala Glu His Ser Gln Arg Asp Asp Arg Trp Leu Leu
 675 680 685
 Val Ala Leu Leu Val Pro Thr Cys Val Phe Leu Val Val Leu Leu Ala
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 Leu Gly Ile Val Tyr Cys Thr Arg Cys Gly Pro His Ala Pro Asn Lys
 705 710 715 720
 Arg Ile Thr Asp Cys Tyr Arg Trp Val Ile His Ala Gly Ser Lys Ser
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 <212> DNA
 <213> Homo sapiens

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 <212> PRT
 <213> Homo sapiens

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35      40      45
Thr Pro Thr Ile Glu Asp Phe His Arg Lys Val Tyr Asn Ile Arg Gly
50      55      60
Asp Met Tyr Gln Leu Asp Ile Leu Asp Thr Ser Gly Asn His Pro Phe
65      70      75      80
Pro Ala Met Arg Arg Leu Ser Ile Leu Thr Gly Asp Val Phe Ile Leu
85      90      95
Val Phe Ser Leu Asp Asn Arg Glu Ser Phe Asp Glu Val Lys Arg Leu
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Gln Lys Gln Ile Leu Glu Val Lys Ser Cys Leu Lys Asn Lys Thr Lys
115      120      125
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145      150      155      160
Ser Gly Asp Glu Asn Cys Ala Tyr Phe Glu Val Ser Ala Lys Lys Asn
165      170      175
Thr Asn Val Asp Glu Met Phe Tyr Val Leu Phe Ser Met Ala Lys Leu
180      185      190
Pro His Glu Met Ser Pro Ala Leu His Arg Lys Ile Ser Val Gln Tyr
195      200      205
Gly Asp Ala Phe His Pro Arg Pro Phe Cys Met Arg Arg Val Lys Glu
210      215      220
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<210> 199
 <211> 2159
 <212> DNA
 <213> Homo sapiens

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<400> 199
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<211> 529

<212> PRT

<213> Homo sapiens

<400> 200

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His	Thr	Glu	Glu	Glu	Val	Glu	Val	Asp	Ser	His	Ala	Tyr	Ser	His
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Ser	Val	Gly	Gln	Asp	Ser	Pro	Glu	Pro	Arg	Ser	Phe	Thr	Asp	Leu
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Leu	Asp	Asp	Gly	Gln	Asp	Asn	Asn	Thr	Gln	Ile	Glu	Glu	Asp	Thr
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His	Asn	Tyr	Tyr	Ile	Ser	Arg	Ile	Tyr	Gly	Pro	Ser	Asp	Ser	Ala
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Arg	Asp	Leu	Trp	Val	Asn	Ile	Asp	Gln	Met	Glu	Lys	Asp	Lys	Val
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<210> 201
<211> 2608
<212> DNA
<213> Homo sapiens
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Phe	Ser	Val	Asp	Ser	Asn	Leu	Leu	Gly	Ser	Leu	Ser	Pro	Lys	Thr	Gly														
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Ser	Val	Gly	Pro	Pro	Val	Ala	Val	Pro	Glu	Pro	Ile	Gly	Phe	Pro	Thr														
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Gln Asp Ser Ser Arg	Cys Val Ala Cys Met	Val Asp Ser Ser Leu Gly
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Asp Thr Phe Glu Gln	Leu Ala Glu Val Asp	Val Thr Pro Pro Val His
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Cys Leu Arg Ile Thr	Ala Leu Leu Val Cys	Glu Glu Leu Leu Trp Val
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His Thr Gly His Val	Arg Phe Leu Ala Ala	Val Gln Leu Pro Asp Gly
1970	1975	1980
Phe Asn Leu Leu Cys	Pro Thr Pro Pro Pro	Pro Pro Asp Thr Gly Pro
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Glu Lys Leu Pro Ser	Leu Glu His Arg Asp	Ser Pro Trp His Arg Gly
2005	2010	2015
Pro Ala Pro Ala Arg	Pro Lys Met Leu Val	Ile Ser Gly Gly Asp Gly
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<212> PRT
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35 40 45
Gln Pro Trp His Ala Ala Leu Pro Ser Ser Pro Ala Pro Ala Pro Ala

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Ala	Leu	Glu	Gly	Phe	Pro	Arg	Leu	Val	Gly	Pro	Asp	Phe	Phe	Gly	Cys		
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<400> 207

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<212> PRT

<213> Homo sapiens

<400> 208

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Pro Ile Ile Lys Phe Pro Gly Asp Val Ala Pro Lys Thr Asp Lys Glu			
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Leu Ala Val Gln Tyr Leu Asn Thr Phe Tyr Gly Cys Pro Lys Glu Ser			
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Cys Asn Leu Phe Val Leu Lys Asp Thr Leu Lys Lys Met Gln Lys Phe			
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Phe Gly Leu Pro Gln Thr Gly Asp Leu Asp Gln Asn Thr Ile Glu Thr			
85	90	95	
Met Arg Lys Pro Arg Cys Gly Asn Pro Asp Val Ala Asn Tyr Asn Phe			
100	105	110	
Phe Pro Arg Lys Pro Lys Trp Asp Lys Asn Gln Ile Thr Tyr Arg Ile			
115	120	125	
Ile Gly Tyr Thr Pro Asp Leu Asp Pro Glu Thr Val Asp Asp Ala Phe			
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Ala Arg Ala Phe Gln Val Trp Ser Asp Val Thr Pro Leu Arg Phe Ser			
145	150	155	160
Arg Ile His Asp Gly Glu Ala Asp Ile Met Ile Asn Phe Gly Arg Trp			
165	170	175	
Glu His Gly Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala			
180	185	190	
His Ala Phe Ala Pro Gly Thr Gly Val Gly Gly Asp Ser His Phe Asp			
195	200	205	
Asp Asp Glu Leu Trp Thr Leu Gly Glu Gly Gln Val Val Arg Val Lys			
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Tyr Gly Asn Ala Asp Gly Glu Tyr Cys Lys Phe Pro Phe Leu Phe Asn			
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Gly Lys Glu Tyr Asn Ser Cys Thr Asp Thr Gly Arg Ser Asp Gly Phe			
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Leu Trp Cys Ser Thr Thr Tyr Asn Phe Glu Lys Asp Gly Lys Tyr Gly			
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Phe Cys Pro His Glu Ala Leu Phe Thr Met Gly Gly Asn Ala Glu Gly			
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Gln Pro Cys Lys Phe Pro Phe Arg Phe Gln Gly Thr Ser Tyr Asp Ser			
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Cys Thr Thr Glu Gly Arg Thr Asp Gly Tyr Arg Trp Cys Gly Thr Thr			
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Glu Asp Tyr Asp Arg Asp Lys Lys Tyr Gly Phe Cys Pro Glu Thr Ala			
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Met Ser Thr Val Gly Gly Asn Ser Glu Gly Ala Pro Cys Val Phe Pro			
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Phe Thr Phe Leu Gly Asn Lys Tyr Glu Ser Cys Thr Ser Ala Gly Arg			
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Ser Asp Gly Lys Met Trp Cys Ala Thr Thr Ala Asn Tyr Asp Asp Asp			
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Arg Lys Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val			
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Pro Gly Ala Leu Met Ala Pro Ile Tyr Thr Tyr Thr Lys Asn Phe Arg			
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Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Glu Leu Tyr Gly Ala Ser			
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Pro Asp Ile Asp Leu Gly Thr Gly Pro Thr Pro Thr Leu Gly Pro Val			
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Thr Pro Glu Ile Cys Lys Gln Asp Ile Val Phe Asp Gly Ile Ala Gln			
465	470	475	480
Ile Arg Gly Glu Ile Phe Phe Phe Lys Asp Arg Phe Ile Trp Arg Thr			
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Val Thr Pro Arg Asp Lys Pro Met Gly Pro Leu Leu Val Ala Thr Phe
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 Trp Pro Glu Leu Pro Glu Lys Ile Asp Ala Val Tyr Glu Ala Pro Gln
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 Asn Lys Lys Thr Tyr Ile Phe Ala Gly Asp Lys Phe Trp Arg Tyr Asn
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 Glu Val Lys Lys Lys Met Asp Pro Gly Phe Pro Lys Leu Ile Ala Asp
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 Gly Gly Gly His Ser Tyr Phe Phe Lys Gly Ala Tyr Tyr Leu Lys Leu
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<210> 209

<211> 4160

<212> DNA

<213> Homo sapiens

<400> 209

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<210> 210
 <211> 328
 <212> PRT
 <213> Homo sapiens

<400> 210

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 Glu Pro Ser Pro Thr Pro Thr Gly Pro Leu Ala Phe Pro Ala Trp Pro
 165 170 175
 Trp Ser Phe Phe His Ser Cys Pro Gly Leu Pro Ala Leu Ser Asn Gln
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 Gly Ala Ser Ser Thr Arg Arg Ala Arg Pro Leu Glu Arg Pro Ala Thr
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 Pro Val Pro Val Ala Pro Ser Ser Arg Ala Ala Arg Ser Ser His Ile
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<211> 5680

<212> DNA

<213> Homo sapiens

<400> 211

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 <212> PRT
 <213> Homo sapiens

<400> 212

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			20					25					30		
Ser	Ile	Arg	Ser	Cys	Lys	Cys	Ser	Gly	Glu	Arg	Pro	Lys	Gly	Leu	Ser
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Gly	Gly	Val	Pro	Gly	Pro	Ala	Arg	Arg	Arg	Val	Val	Cys	Ser	Gly	Gly
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Asp	Leu	Pro	Glu	Pro	Pro	Glu	Pro	Gly	Leu	Leu	Pro	Asn	Gly	Thr	Val
65					70					75					80
Thr	Leu	Leu	Leu	Ser	Asn	Asn	Lys	Ile	Thr	Gly	Leu	Arg	Asn	Gly	Ser
				85					90					95	
Phe	Leu	Gly	Leu	Ser	Leu	Leu	Glu	Lys	Leu	Asp	Leu	Arg	Asn	Asn	Ile
			100					105						110	
Ile	Ser	Thr	Val	Gln	Pro	Gly	Ala	Phe	Leu	Gly	Leu	Gly	Glu	Leu	Lys
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Arg	Leu	Asp	Leu	Ser	Asn	Asn	Arg	Ile	Gly	Cys	Leu	Thr	Ser	Glu	Thr
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Phe	Ser	Ser	Leu	Gln	Pro	Gly	Val	Phe	Asp	Glu	Leu	Pro	Ala	Leu	Lys
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Val	Val	Asp	Leu	Gly	Thr	Glu	Phe	Leu	Thr	Cys	Asp	Cys	His	Leu	Arg
			180					185					190		
Trp	Leu	Leu	Pro	Trp	Ala	Gln	Asn	Arg	Ser	Leu	Gln	Leu	Ser	Glu	His
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Thr	Leu	Cys	Ala	Tyr	Pro	Ser	Ala	Leu	His	Ala	Gln	Ala	Leu	Gly	Ser
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Leu	Gln	Glu	Ala	Gln	Leu	Cys	Cys	Glu	Gly	Ala	Leu	Glu	Leu	His	Thr
225					230					235					240
His	His	Leu	Ile	Pro	Ser	Leu	Arg	Gln	Val	Val	Phe	Gln	Gly	Asp	Arg
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Leu	Pro	Phe	Gln	Cys	Ser	Ala	Ser	Tyr	Leu	Gly	Asn	Asp	Thr	Arg	Ile
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Arg	Trp	Tyr	His	Asn	Arg	Ala	Pro	Val	Glu	Gly	Asp	Glu	Gln	Ala	Gly
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Ile	Leu	Leu	Ala	Glu	Ser	Leu	Ile	His	Asp	Cys	Thr	Phe	Ile	Thr	Ser
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Glu	Leu	Thr	Leu	Ser	His	Ile	Gly	Val	Trp	Ala	Ser	Gly	Glu	Trp	Glu
305					310					315					320
Cys	Thr	Val	Ser	Met	Ala	Gln	Gly	Asn	Ala	Ser	Lys	Lys	Val	Glu	Ile
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Val	Val	Leu	Glu	Thr	Ser	Ala	Ser	Tyr	Cys	Pro	Ala	Glu	Arg	Val	Ala
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Ala Tyr Gln Ser Cys Leu Gln Tyr Pro Phe Thr Ser Val Pro Leu Gly
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 Gly Gly Ala Pro Gly Thr Arg Ala Ser Arg Arg Cys Asp Arg Ala Gly
 385 390 395 400
 Arg Trp Glu Pro Gly Asp Tyr Ser His Cys Leu Tyr Thr Asn Asp Ile
 405 410 415
 Thr Arg Val Leu Tyr Thr Phe Val Leu Met Pro Ile Asn Ala Ser Asn
 420 425 430
 Ala Leu Thr Leu Ala His Gln Leu Arg Val Tyr Thr Ala Glu Ala Ala
 435 440 445
 Ser Phe Ser Asp Met Met Asp Val Val Tyr Val Ala Gln Met Ile Gln
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 Lys Phe Leu Gly Tyr Val Asp Gln Ile Lys Glu Leu Val Glu Val Met
 465 470 475 480
 Val Asp Met Ala Ser Asn Leu Met Leu Val Asp Glu His Leu Leu Trp
 485 490 495
 Leu Ala Gln Arg Glu Asp Lys Ala Cys Ser Arg Ile Val Gly Ala Leu
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 Glu Arg Ile Gly Gly Ala Ala Leu Ser Pro His Ala Gln His Ile Ser
 515 520 525
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 Ser Tyr Val Gly Leu Thr Cys Thr Ala Phe Gln Arg Arg Glu Gly Gly
 545 550 555 560
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 565 570 575
 Pro Glu Pro Pro Ala Asp Gln Gln Leu Arg Phe Arg Cys Thr Thr Gly
 580 585 590
 Arg Pro Asn Val Ser Leu Ser Ser Phe His Ile Lys Asn Ser Val Ala
 595 600 605
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 610 615 620
 Ala Leu Ala Pro Pro Val Pro Pro Asp Cys Thr Leu Gln Leu Leu Val
 625 630 635 640
 Phe Arg Asn Gly Arg Leu Phe His Ser His Ser Asn Thr Ser Arg Pro
 645 650 655
 Gly Ala Ala Gly Pro Gly Lys Arg Arg Gly Val Ala Thr Pro Val Ile
 660 665 670
 Phe Ala Gly Thr Ser Gly Cys Gly Val Gly Asn Leu Thr Glu Pro Val
 675 680 685
 Ala Val Ser Leu Arg His Trp Ala Glu Gly Ala Glu Pro Val Ala Ala
 690 695 700
 Trp Trp Ser Gln Glu Gly Pro Gly Glu Ala Gly Gly Trp Thr Ser Glu
 705 710 715 720
 Gly Cys Gln Leu Arg Ser Ser Gln Pro Asn Val Ser Ala Leu His Cys
 725 730 735
 Gln His Leu Gly Asn Val Ala Val Leu Met Glu Leu Ser Ala Phe Pro
 740 745 750
 Arg Glu Val Gly Gly Ala Gly Ala Gly Leu His Pro Val Val Tyr Pro
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 Cys Thr Ala Leu Leu Leu Leu Cys Leu Phe Ala Thr Ile Ile Thr Tyr
 770 775 780
 Ile Leu Asn His Ser Ser Ile Arg Val Ser Arg Lys Gly Trp His Met
 785 790 795 800
 Leu Leu Asn Leu Cys Phe His Ile Ala Met Thr Ser Ala Val Phe Ala
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 Gly Gly Ile Thr Leu Thr Asn Tyr Gln Met Val Cys Gln Ala Val Gly
 820 825 830
 Ile Thr Leu His Tyr Ser Ser Leu Ser Thr Leu Leu Trp Met Gly Val
 835 840 845
 Lys Ala Arg Val Leu His Lys Glu Leu Thr Trp Arg Ala Pro Pro Pro

850		855		860	
Gln Glu Gly Asp Pro Ala Leu Pro Thr Pro Ser Pro Met Leu Arg Phe					
865		870		875	880
Tyr Leu Ile Ala Gly Gly Ile Pro Leu Ile Ile Cys Gly Ile Thr Ala					
	885		890		895
Ala Val Asn Ile His Asn Tyr Arg Asp His Ser Pro Tyr Cys Trp Leu					
	900		905		910
Val Trp Arg Pro Ser Leu Gly Ala Phe Tyr Ile Pro Val Ala Leu Ile					
	915		920		925
Leu Leu Ile Thr Trp Ile Tyr Phe Leu Cys Ala Gly Leu Arg Leu Arg					
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Gly Pro Leu Ala Gln Asn Pro Lys Ala Gly Asn Ser Arg Ala Ser Leu					
945		950		955	960
Glu Ala Gly Glu Glu Leu Arg Gly Ser Thr Arg Leu Arg Gly Ser Gly					
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Pro Leu Leu Ser Asp Ser Gly Ser Leu Leu Ala Thr Gly Ser Ala Arg					
	980		985		990
Val Gly Thr Pro Gly Pro Pro Glu Asp Gly Asp Ser Leu Tyr Ser Pro					
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Gly Val Gln Leu Gly Ala Leu Val Thr Thr His Phe Leu Tyr Leu Ala					
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Met Trp Ala Cys Gly Ala Leu Ala Val Ser Gln Arg Trp Leu Pro Arg					
1025		1030		1035	1040
Val Val Cys Ser Cys Leu Tyr Gly Val Ala Ala Ser Ala Leu Gly Leu					
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Phe Val Phe Thr His His Cys Ala Arg Arg Arg Asp Val Arg Ala Ser					
	1060		1065		1070
Trp Arg Ala Cys Cys Pro Pro Ala Ser Pro Ala Ala Pro His Ala Pro					
	1075		1080		1085
Pro Arg Ala Leu Pro Ala Ala Ala Glu Asp Gly Ser Pro Val Phe Gly					
	1090		1095		1100
Glu Gly Pro Pro Ser Leu Lys Ser Ser Pro Ser Gly Ser Ser Gly His					
1105		1110		1115	1120
Pro Leu Ala Leu Gly Pro Cys Lys Leu Thr Asn Leu Gln Leu Ala Gln					
	1125		1130		1135
Ser Gln Val Cys Glu Ala Gly Ala Ala Gly Gly Glu Gly Glu Pro					
	1140		1145		1150
Glu Pro Ala Gly Thr Arg Gly Asn Leu Ala His Arg His Pro Asn Asn					
	1155		1160		1165
Val His His Gly Arg Arg Ala His Lys Ser Arg Ala Lys Gly His Arg					
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Ala Gly Glu Ala Cys Gly Lys Asn Arg Leu Lys Ala Leu Arg Gly Gly					
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Ala Ala Gly Ala Leu Glu Leu Leu Ser Ser Glu Ser Gly Ser Leu His					
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Asn Ser Pro Thr Asp Ser Tyr Leu Gly Ser Ser Arg Asn Ser Pro Gly					
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Ala Gly Leu Gln Leu Glu Gly Glu Pro Met Leu Thr Pro Ser Glu Gly					
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Ser Asp Thr Ser Ala Ala Pro Leu Ser Glu Ala Gly Arg Ala Gly Gln					
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Arg Arg Ser Ala Ser Arg Asp Ser Leu Lys Gly Gly Gly Ala Leu Glu					
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Lys Glu Ser His Arg Arg Ser Tyr Pro Leu Asn Ala Ala Ser Leu Asn					
	1285		1290		1295
Gly Ala Pro Lys Gly Gly Lys Tyr Asp Asp Val Thr Leu Met Gly Ala					
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Thr Thr Val					
1330					

<210> 213
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 <212> DNA
 <213> Homo sapiens

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 gcatgtctaa gtgctagaca tgctcagctt tgtggatacg cggactttgt tgctgcttgc 180
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<210> 214

<211> 1366

<212> PRT

<213> Homo sapiens

<400> 214

Met	Leu	Ser	Phe	Val	Asp	Thr	Arg	Thr	Leu	Leu	Leu	Leu	Ala	Val	Thr
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			20					25					30		
Gly	Pro	Ala	Gly	Asp	Arg	Gly	Pro	Arg	Gly	Glu	Arg	Gly	Pro	Pro	Gly
		35					40					45			
Pro	Pro	Gly	Arg	Asp	Gly	Glu	Asp	Gly	Pro	Thr	Gly	Pro	Pro	Gly	Pro
		50				55					60				
Pro	Gly	Pro	Pro	Gly	Pro	Pro	Gly	Leu	Gly	Gly	Asn	Phe	Ala	Ala	Gln
		65			70				75					80	
Tyr	Asp	Gly	Lys	Gly	Val	Gly	Leu	Gly	Pro	Gly	Pro	Met	Gly	Leu	Met
			85					90						95	
Gly	Pro	Arg	Gly	Pro	Pro	Gly	Ala	Ala	Gly	Ala	Pro	Gly	Pro	Gln	Gly
			100					105						110	
Phe	Gln	Gly	Pro	Ala	Gly	Glu	Pro	Gly	Glu	Pro	Gly	Gln	Thr	Gly	Pro
		115					120					125			

Ala Gly Ala Arg Gly Pro Ala Gly Pro Pro Gly Lys Ala Gly Glu Asp
 130 135 140
 Gly His Pro Gly Lys Pro Gly Arg Pro Gly Glu Arg Gly Val Val Gly
 145 150 155 160
 Pro Gln Gly Ala Arg Gly Phe Pro Gly Thr Pro Gly Leu Pro Gly Phe
 165 170 175
 Lys Gly Ile Arg Gly His Asn Gly Leu Asp Gly Leu Lys Gly Gln Pro
 180 185 190
 Gly Ala Pro Gly Val Lys Gly Glu Pro Gly Ala Pro Gly Glu Asn Gly
 195 200 205
 Thr Pro Gly Gln Thr Gly Ala Arg Gly Leu Pro Gly Glu Arg Gly Arg
 210 215 220
 Val Gly Ala Pro Gly Pro Ala Gly Ala Arg Gly Ser Asp Gly Ser Val
 225 230 235 240
 Gly Pro Val Gly Pro Ala Gly Pro Ile Gly Ser Ala Gly Pro Pro Gly
 245 250 255
 Phe Pro Gly Ala Pro Gly Pro Lys Gly Glu Ile Gly Ala Val Gly Asn
 260 265 270
 Ala Gly Pro Ala Gly Pro Ala Gly Pro Arg Gly Glu Val Gly Leu Pro
 275 280 285
 Gly Leu Ser Gly Pro Val Gly Pro Pro Gly Asn Pro Gly Ala Asn Gly
 290 295 300
 Leu Thr Gly Ala Lys Gly Ala Ala Gly Leu Pro Gly Val Ala Gly Ala
 305 310 315 320
 Pro Gly Leu Pro Gly Pro Arg Gly Ile Pro Gly Pro Val Gly Ala Ala
 325 330 335
 Gly Ala Thr Gly Ala Arg Gly Leu Val Gly Glu Pro Gly Pro Ala Gly
 340 345 350
 Ser Lys Gly Glu Ser Gly Asn Lys Gly Glu Pro Gly Ser Ala Gly Pro
 355 360 365
 Gln Gly Pro Pro Gly Pro Ser Gly Glu Glu Gly Lys Arg Gly Pro Asn
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 Gly Glu Ala Gly Ser Ala Gly Pro Pro Gly Pro Gly Leu Arg Gly
 385 390 395 400
 Ser Pro Gly Ser Arg Gly Leu Pro Gly Ala Asp Gly Arg Ala Gly Val
 405 410 415
 Met Gly Pro Pro Gly Ser Arg Gly Ala Ser Gly Pro Ala Gly Val Arg
 420 425 430
 Gly Pro Asn Gly Asp Ala Gly Arg Pro Gly Glu Pro Gly Leu Met Gly
 435 440 445
 Pro Arg Gly Leu Pro Gly Ser Pro Gly Asn Ile Gly Pro Ala Gly Lys
 450 455 460
 Glu Gly Pro Val Gly Leu Pro Gly Ile Asp Gly Arg Pro Gly Pro Ile
 465 470 475 480
 Gly Pro Ala Gly Ala Arg Gly Glu Pro Gly Asn Ile Gly Phe Pro Gly
 485 490 495
 Pro Lys Gly Pro Thr Gly Asp Pro Gly Lys Asn Gly Asp Lys Gly His
 500 505 510
 Ala Gly Leu Ala Gly Ala Arg Gly Ala Pro Gly Pro Asp Gly Asn Asn
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 Gly Ala Gln Gly Pro Pro Gly Pro Gln Gly Val Gln Gly Gly Lys Gly
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 Glu Gln Gly Pro Ala Gly Pro Pro Gly Phe Gln Gly Leu Pro Gly Pro
 545 550 555 560
 Ser Gly Pro Ala Gly Glu Val Gly Lys Pro Gly Glu Arg Gly Leu His
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 Gly Glu Phe Gly Leu Pro Gly Pro Ala Gly Pro Arg Gly Glu Arg Gly
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 Pro Pro Gly Glu Ser Gly Ala Ala Gly Pro Thr Gly Pro Ile Gly Ser
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Lys Gly Glu Pro Gly Leu Arg Gly Glu Ile Gly Asn Pro Gly Arg Asp				
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Gly Leu Arg Gly Pro Arg Gly Asp Gln Gly Pro Val Gly Arg Thr Gly				
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Glu Val Gly Ala Val Gly Pro Pro Gly Phe Ala Gly Glu Lys Gly Pro				
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Ser Gly Glu Ala Gly Thr Ala Gly Pro Pro Gly Thr Pro Gly Pro Gln				
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Gly Leu Leu Gly Ala Pro Gly Ile Leu Gly Leu Pro Gly Ser Arg Gly				
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Glu Arg Gly Leu Pro Gly Val Ala Gly Ala Val Gly Glu Pro Gly Pro				
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Gly Glu Pro Gly Glu Lys Gly Pro Arg Gly Leu Pro Gly Leu Lys Gly				
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His Asn Gly Leu Gln Gly Leu Pro Gly Ile Ala Gly His His Gly Asp				
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Gly Pro Ser Gly Pro Ala Gly Lys Asp Gly Arg Thr Gly His Pro Gly				
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Thr Val Gly Pro Ala Gly Ile Arg Gly Pro Gln Gly His Gln Gly Pro				
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Ala Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Gly Val Ser				
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Gly Gly Gly Tyr Asp Phe Gly Tyr Asp Gly Asp Phe Tyr Arg Ala Asp
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<211> 4898

<212> DNA

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 Phe Tyr Asp Arg Ser Asp Ile Asp Ala Val Tyr Val Thr Thr Asn Gly
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 Ile Ile Ala Thr Ser Glu Pro Pro Ala Lys Glu Ser His Pro Gly Leu
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 Thr Thr Asp Gly Leu Gly Lys Val Tyr Tyr Arg Glu Asp Leu Ser Pro
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 Ser Ile Thr Gln Arg Ala Ala Glu Cys Val His Arg Gly Phe Pro Glu
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 Ile Ser Phe Gln Pro Ser Ser Ala Val Val Val Thr Trp Glu Ser Val
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 Ala Pro Tyr Gln Gly Pro Ser Arg Asp Pro Asp Gln Lys Gly Lys Arg
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 Asn Thr Phe Gln Ala Val Leu Ala Ser Ser Asp Ser Ser Ser Tyr Ala
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 Ile Phe Leu Tyr Pro Glu Asp Gly Leu Gln Phe His Thr Thr Phe Ser
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 Lys Lys Glu Asn Asn Gln Val Pro Ala Val Val Ala Phe Ser Gln Gly
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 Ser Val Gly Phe Leu Trp Lys Ser Asn Gly Ala Tyr Asn Ile Phe Ala
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 Asn Asp Arg Glu Ser Ile Glu Asn Leu Ala Lys Ser Ser Asn Ser Gly
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 Gln Gln Gly Val Trp Val Phe Glu Ile Gly Ser Pro Ala Thr Thr Asn
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 Tyr Asp Asp Glu Asp Glu Asp Tyr Asp Leu Ala Thr Thr Arg Leu Gly
 290 295 300
 Leu Glu Asp Val Gly Thr Thr Pro Phe Ser Tyr Lys Ala Leu Arg Arg
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 Gly Gly Ala Asp Thr Tyr Ser Val Pro Ser Val Leu Ser Pro Arg Arg
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 Ala Ala Thr Glu Arg Pro Leu Gly Pro Pro Thr Glu Arg Thr Arg Ser
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 Phe Gln Leu Ala Val Glu Thr Phe His Gln Gln His Pro Gln Val Ile
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 Asp Val Asp Glu Val Glu Glu Thr Gly Val Val Phe Ser Tyr Asn Thr
 370 375 380
 Asp Ser Arg Gln Thr Cys Ala Asn Asn Arg His Gln Cys Ser Val His
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 Ala Glu Cys Arg Asp Tyr Ala Thr Gly Phe Cys Cys Ser Cys Val Ala
 405 410 415
 Gly Tyr Thr Gly Asn Gly Arg Gln Cys Val Ala Glu Gly Ser Pro Gln

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Cys	Asp	Ile	Pro																	

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Val	Gly	Gln	Phe	Pro	Val	Val	Arg	Asp	Phe	Leu	Tyr	Lys	Ile	Ile	Asp	
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Leu																			

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 35 40 45
 His Phe Ala Ile Ser Glu Tyr Asn Lys Ala Thr Glu Asp Glu Tyr Tyr
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 Arg Arg Pro Leu Gln Val Leu Arg Ala Arg Glu Gln Thr Phe Gly Gly
 65 70 75 80
 Val Asn Tyr Phe Phe Asp Val Glu Val Gly Arg Thr Ile Cys Thr Lys
 85 90 95
 Ser Gln Pro Asn Leu Asp Thr Cys Ala Phe His Glu Gln Pro Glu Leu
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 Gln Lys Lys Gln Leu Cys Ser Phe Glu Ile Tyr Glu Val Pro Trp Glu
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<210> 224
 <211> 141
 <212> PRT
 <213> Homo sapiens

<400> 224
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 35 40 45
 His Phe Ala Ile Ser Glu Tyr Asn Lys Ala Thr Lys Asp Asp Tyr Tyr
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 Arg Arg Pro Leu Arg Val Leu Arg Ala Arg Gln Gln Thr Val Gly Gly

65					70					75				80
Val	Asn	Tyr	Phe	Phe	Asp	Val	Glu	Val	Gly	Arg	Thr	Ile	Cys	Thr
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Ser	Gln	Pro	Asn	Leu	Asp	Thr	Cys	Ala	Phe	His	Glu	Gln	Pro	Glu
			100					105				110		
Gln	Lys	Lys	Gln	Leu	Cys	Ser	Phe	Glu	Ile	Tyr	Glu	Val	Pro	Trp
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<210> 225
 <211> 5460
 <212> DNA
 <213> Homo sapiens

<400> 225

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<210> 226

<211> 1466

<212> PRT

<213> Homo sapiens

<400> 226

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			20				25				30				
Ser	His	Leu	Gly	Gln	Ser	Tyr	Ala	Asp	Arg	Asp	Val	Trp	Lys	Pro	Glu

35					40					45					
Pro	Cys	Gln	Ile	Cys	Val	Cys	Asp	Ser	Gly	Ser	Val	Leu	Cys	Asp	Asp
50						55					60				
Ile	Ile	Cys	Asp	Asp	Gln	Glu	Leu	Asp	Cys	Pro	Asn	Pro	Glu	Ile	Pro
65					70					75					80
Phe	Gly	Glu	Cys	Cys	Ala	Val	Cys	Pro	Gln	Gly	Pro	Pro	Thr	Ala	Pro
				85					90						95
Arg	Pro	Pro	Asn	Gly	Gln	Gly	Pro	Gln	Gly	Pro	Lys	Gly	Asp	Pro	Gly
			100					105					110		
Pro	Pro	Gly	Ile	Pro	Gly	Arg	Asn	Gly	Asp	Pro	Gly	Ile	Pro	Gly	Gln
		115					120					125			
Pro	Gly	Ser	Pro	Gly	Ser	Pro	Gly	Pro	Pro	Gly	Ile	Cys	Glu	Ser	Cys
130						135					140				
Pro	Thr	Gly	Pro	Gln	Asn	Tyr	Ser	Pro	Gln	Tyr	Asp	Ser	Tyr	Asp	Val
145					150					155					160
Lys	Ser	Gly	Val	Ala	Val	Gly	Gly	Leu	Ala	Gly	Tyr	Pro	Gly	Pro	Ala
				165					170						175
Gly	Pro	Pro	Gly	Pro	Pro	Gly	Pro	Pro	Gly	Thr	Ser	Gly	His	Pro	Gly
			180					185					190		
Ser	Pro	Gly	Ser	Pro	Gly	Tyr	Gln	Gly	Pro	Pro	Gly	Glu	Pro	Gly	Gln
		195					200					205			
Ala	Gly	Pro	Ser	Gly	Pro	Pro	Gly	Pro	Pro	Gly	Ala	Ile	Gly	Pro	Ser
210						215					220				
Gly	Pro	Ala	Gly	Lys	Asp	Gly	Glu	Ser	Gly	Arg	Pro	Gly	Arg	Pro	Gly
225					230					235					240
Glu	Arg	Gly	Leu	Pro	Gly	Pro	Pro	Gly	Ile	Lys	Gly	Pro	Ala	Gly	Ile
				245					250						255
Pro	Gly	Phe	Pro	Gly	Met	Lys	Gly	His	Arg	Gly	Phe	Asp	Gly	Arg	Asn
		260						265					270		
Gly	Glu	Lys	Gly	Glu	Thr	Gly	Ala	Pro	Gly	Leu	Lys	Gly	Glu	Asn	Gly
		275					280						285		
Leu	Pro	Gly	Glu	Asn	Gly	Ala	Pro	Gly	Pro	Met	Gly	Pro	Arg	Gly	Ala
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Pro	Gly	Glu	Arg	Gly	Arg	Pro	Gly	Leu	Pro	Gly	Ala	Ala	Gly	Ala	Arg
305					310					315					320
Gly	Asn	Asp	Gly	Ala	Arg	Gly	Ser	Asp	Gly	Gln	Pro	Gly	Pro	Pro	Gly
				325					330					335	
Pro	Pro	Gly	Thr	Ala	Gly	Phe	Pro	Gly	Ser	Pro	Gly	Ala	Lys	Gly	Glu
			340					345					350		
Val	Gly	Pro	Ala	Gly	Ser	Pro	Gly	Ser	Asn	Gly	Ala	Pro	Gly	Gln	Arg
		355						360					365		
Gly	Glu	Pro	Gly	Pro	Gln	Gly	His	Ala	Gly	Ala	Gln	Gly	Pro	Pro	Gly
		370				375					380				
Pro	Pro	Gly	Ile	Asn	Gly	Ser	Pro	Gly	Gly	Lys	Gly	Glu	Met	Gly	Pro
385					390					395					400
Ala	Gly	Ile	Pro	Gly	Ala	Pro	Gly	Leu	Met	Gly	Ala	Arg	Gly	Pro	Pro
				405				410					415		
Gly	Pro	Ala	Gly	Ala	Asn	Gly	Ala	Pro	Gly	Leu	Arg	Gly	Gly	Ala	Gly
		420						425					430		
Glu	Pro	Gly	Lys	Asn	Gly	Ala	Lys	Gly	Glu	Pro	Gly	Pro	Arg	Gly	Glu
		435					440						445		
Arg	Gly	Glu	Ala	Gly	Ile	Pro	Gly	Val	Pro	Gly	Ala	Lys	Gly	Glu	Asp
		450				455					460				
Gly	Lys	Asp	Gly	Ser	Pro	Gly	Glu	Pro	Gly	Ala	Asn	Gly	Leu	Pro	Gly
465					470					475					480
Ala	Ala	Gly	Glu	Arg	Gly	Ala	Pro	Gly	Phe	Arg	Gly	Pro	Ala	Gly	Pro
				485					490					495	
Asn	Gly	Ile	Pro	Gly	Glu	Lys	Gly	Pro	Ala	Gly	Glu	Arg	Gly	Ala	Pro
			500					505					510		
Gly	Pro	Ala	Gly	Pro	Arg	Gly	Ala	Ala	Gly	Glu	Pro	Gly	Arg	Asp	Gly
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Val Pro Gly Gly Pro Gly Met Arg Gly Met Pro Gly Ser Pro Gly Gly
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 Pro Gly Ser Asp Gly Lys Pro Gly Pro Pro Gly Ser Gln Gly Glu Ser
 545 550 555 560
 Gly Arg Pro Gly Pro Pro Gly Pro Ser Gly Pro Arg Gly Gln Pro Gly
 565 570 575
 Val Met Gly Phe Pro Gly Pro Lys Gly Asn Asp Gly Ala Pro Gly Lys
 580 585 590
 Asn Gly Glu Arg Gly Gly Pro Gly Gly Pro Gly Pro Gln Gly Pro Pro
 595 600 605
 Gly Lys Asn Gly Glu Thr Gly Pro Gln Gly Pro Pro Gly Pro Thr Gly
 610 615 620
 Pro Gly Gly Asp Lys Gly Asp Thr Gly Pro Pro Gly Pro Gln Gly Leu
 625 630 635 640
 Gln Gly Leu Pro Gly Thr Gly Gly Pro Pro Gly Glu Asn Gly Lys Pro
 645 650 655
 Gly Glu Pro Gly Pro Lys Gly Asp Ala Gly Ala Pro Gly Ala Pro Gly
 660 665 670
 Gly Lys Gly Asp Ala Gly Ala Pro Gly Glu Arg Gly Pro Pro Gly Leu
 675 680 685
 Ala Gly Ala Pro Gly Leu Arg Gly Gly Ala Gly Pro Pro Gly Pro Glu
 690 695 700
 Gly Gly Lys Gly Ala Ala Gly Pro Pro Gly Pro Pro Gly Ala Ala Gly
 705 710 715 720
 Thr Pro Gly Leu Gln Gly Met Pro Gly Glu Arg Gly Gly Leu Gly Ser
 725 730 735
 Pro Gly Pro Lys Gly Asp Lys Gly Glu Pro Gly Gly Pro Gly Ala Asp
 740 745 750
 Gly Val Pro Gly Lys Asp Gly Pro Arg Gly Pro Thr Gly Pro Ile Gly
 755 760 765
 Pro Pro Gly Pro Ala Gly Gln Pro Gly Asp Lys Gly Glu Gly Ala
 770 775 780
 Pro Gly Leu Pro Gly Ile Ala Gly Pro Arg Gly Ser Pro Gly Glu Arg
 785 790 795 800
 Gly Glu Thr Gly Pro Pro Gly Pro Ala Gly Phe Pro Gly Ala Pro Gly
 805 810 815
 Gln Asn Gly Glu Pro Gly Gly Lys Gly Glu Arg Gly Ala Pro Gly Glu
 820 825 830
 Lys Gly Glu Gly Gly Pro Pro Gly Val Ala Gly Pro Pro Gly Gly Ser
 835 840 845
 Gly Pro Ala Gly Pro Pro Gly Pro Gln Gly Val Lys Gly Glu Arg Gly
 850 855 860
 Ser Pro Gly Gly Pro Gly Ala Ala Gly Phe Pro Gly Ala Arg Gly Leu
 865 870 875 880
 Pro Gly Pro Pro Gly Ser Asn Gly Asn Pro Gly Pro Pro Gly Pro Ser
 885 890 895
 Gly Ser Pro Gly Lys Asp Gly Pro Pro Gly Pro Ala Gly Asn Thr Gly
 900 905 910
 Ala Pro Gly Ser Pro Gly Val Ser Gly Pro Lys Gly Asp Ala Gly Gln
 915 920 925
 Pro Gly Glu Lys Gly Ser Pro Gly Ala Gln Gly Pro Pro Gly Ala Pro
 930 935 940
 Gly Pro Leu Gly Ile Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala Gly
 945 950 955 960
 Pro Pro Gly Met Pro Gly Pro Arg Gly Ser Pro Gly Pro Gln Gly Val
 965 970 975
 Lys Gly Glu Ser Gly Lys Pro Gly Ala Asn Gly Leu Ser Gly Glu Arg
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 Gly Pro Pro Gly Pro Gln Gly Leu Pro Gly Leu Ala Gly Thr Ala Gly
 995 1000 1005
 Glu Pro Gly Arg Asp Gly Asn Pro Gly Ser Asp Gly Leu Pro Gly Arg

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Asp Gly Ser Pro Gly Gly Lys Gly Asp Arg Gly Glu Asn Gly Ser Pro		
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Gly Ala Pro Gly Ala Pro Gly His Pro Gly Pro Pro Gly Pro Val Gly		
	1045	1050
Pro Ala Gly Lys Ser Gly Asp Arg Gly Glu Ser Gly Pro Ala Gly Pro		
	1060	1065
Ala Gly Ala Pro Gly Pro Ala Gly Ser Arg Gly Ala Pro Gly Pro Gln		
	1075	1080
Gly Pro Arg Gly Asp Lys Gly Glu Thr Gly Glu Arg Gly Ala Ala Gly		
	1090	1095
Ile Lys Gly His Arg Gly Phe Pro Gly Asn Pro Gly Ala Pro Gly Ser		
1105	1110	1115
Pro Gly Pro Ala Gly Gln Gln Gly Ala Ile Gly Ser Pro Gly Pro Ala		
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Gly Pro Arg Gly Pro Val Gly Pro Ser Gly Pro Pro Gly Lys Asp Gly		
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Thr Ser Gly His Pro Gly Pro Ile Gly Pro Pro Gly Pro Arg Gly Asn		
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Arg Gly Glu Arg Gly Ser Glu Gly Ser Pro Gly His Pro Gly Gln Pro		
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Gly Pro Pro Gly Pro Pro Gly Ala Pro Gly Pro Cys Cys Gly Gly Val		
1185	1190	1195
Gly Ala Ala Ala Ile Ala Gly Ile Gly Gly Glu Lys Ala Gly Gly Phe		
	1205	1210
Ala Pro Tyr Tyr Gly Asp Glu Pro Met Asp Phe Lys Ile Asn Thr Asp		
	1220	1225
Glu Ile Met Thr Ser Leu Lys Ser Val Asn Gly Gln Ile Glu Ser Leu		
	1235	1240
Ile Ser Pro Asp Gly Ser Arg Lys Asn Pro Ala Arg Asn Cys Arg Asp		
	1250	1255
Leu Lys Phe Cys His Pro Glu Leu Lys Ser Gly Glu Tyr Trp Val Asp		
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Pro Asn Gln Gly Cys Lys Leu Asp Ala Ile Lys Val Phe Cys Asn Met		
	1285	1290
Glu Thr Gly Glu Thr Cys Ile Ser Ala Asn Pro Leu Asn Val Pro Arg		
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Lys His Trp Trp Thr Asp Ser Ser Ala Glu Lys Lys His Val Trp Phe		
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Gly Glu Ser Met Asp Gly Gly Phe Gln Phe Ser Tyr Gly Asn Pro Glu		
	1330	1335
Leu Pro Glu Asp Val Leu Asp Val Gln Leu Ala Phe Leu Arg Leu Leu		
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Ser Ser Arg Ala Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Ile		
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Ala Tyr Met Asp Gln Ala Ser Gly Asn Val Lys Lys Ala Leu Lys Leu		
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Met Gly Ser Asn Glu Gly Glu Phe Lys Ala Glu Gly Asn Ser Lys Phe		
	1395	1400
Thr Tyr Thr Val Leu Glu Asp Gly Cys Thr Lys His Thr Gly Glu Trp		
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Ser Lys Thr Val Phe Glu Tyr Arg Thr Arg Lys Ala Val Arg Leu Pro		
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<210> 227

<211> 6663

<212> DNA

<213> Homo sapiens

<400> 227

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<210> 230

<211> 500

<212> PRT

<213> Homo sapiens

<400> 230

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Ser Gly Trp Ala Ala Lys Gly Thr Val Arg Gly Trp Asn Arg Arg Ala
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Arg Glu Ser Pro Gly His Val Ser Glu Pro Asp Arg Thr Gln Leu Ser
50     55     60
Gln Asp Leu Gly Gly Gly Thr Leu Ala Met Asp Thr Leu Pro Asp Asn
65     70     75     80
Arg Thr Arg Val Val Glu Asp Asn His Ser Tyr Tyr Val Ser Arg Leu
85     90     95
Tyr Gly Pro Ser Glu Pro His Ser Arg Glu Leu Trp Val Asp Val Ala
100    105    110
Glu Ala Asn Arg Ser Gln Val Lys Ile His Thr Ile Leu Ser Asn Thr
115    120    125
His Arg Gln Ala Ser Arg Val Val Leu Ser Phe Asp Phe Pro Phe Tyr
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Gly His Pro Leu Arg Gln Ile Thr Ile Ala Thr Gly Gly Phe Ile Phe
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Met Gly Asp Val Ile His Arg Met Leu Thr Ala Thr Gln Tyr Val Ala
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Pro Leu Met Ala Asn Phe Asn Pro Gly Tyr Ser Asp Asn Ser Thr Val
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Val Tyr Phe Asp Asn Gly Thr Val Phe Val Val Gln Trp Asp His Val
195    200    205
Tyr Leu Gln Gly Trp Glu Asp Lys Gly Ser Phe Thr Phe Gln Ala Ala
210    215    220
Leu His His Asp Gly Arg Ile Val Phe Ala Tyr Lys Glu Ile Pro Met
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Ser Asp Ala Phe Met Ile Leu Asn Pro Ser Pro Asp Val Pro Glu Ser
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Lys Val Thr Ser Met Ser Ala Val Glu Phe Thr Pro Leu Pro Thr Cys

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<211> 5540

<212> DNA

<213> Homo sapiens

<400> 231

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 <212> PRT
 <213> Homo sapiens

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Ile	Ile	Ala	Leu	Thr	Asp	Gly	Glu	Leu	His	Glu	Asp	Leu	Phe	Phe	Tyr
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Ser	Glu	Arg	Glu	Ala	Asn	Arg	Ser	Arg	Asp	Leu	Gly	Ala	Ile	Val	Tyr
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Leu Asn Asn Ala Tyr His Thr Ser Ser Pro Pro Pro Ala Pro Ile Tyr				
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Thr Pro Pro Pro Ala Pro His Cys Pro Pro Pro Pro Pro Ser Ala				
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 Phe Arg Ala Leu Arg Asp Leu Glu Ile Leu Thr Leu Asn Asn Asn Asn
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 Thr Leu Arg Leu His Ser Asn His Leu Tyr Cys Asp Cys His Leu Ala
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 Leu Cys Met Ala Pro Val His Leu Arg Gly Phe Asn Val Ala Asp Val
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 Cys Asn Ala Asn Ser Ile Ser Cys Pro Ser Pro Cys Thr Cys Ser Asn
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<211> 4227

<212> DNA

<213> Homo sapiens

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<212> PRT

<213> Homo sapiens

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<211> 1179

<212> PRT

<213> Homo sapiens

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Gly Glu Arg Gly Leu Pro Gly Leu Gln Gly Val Ile Gly Phe Pro Gly
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Met Gln Gly Pro Glu Gly Pro Gln Gly Pro Pro Gly Gln Lys Gly Asp
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Thr Gly Glu Pro Gly Leu Pro Gly Thr Lys Gly Thr Arg Gly Pro Pro
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Gly Ala Ser Gly Tyr Pro Gly Asn Pro Gly Leu Pro Gly Ile Pro Gly
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Gln Asp Gly Pro Pro Gly Pro Pro Gly Ile Pro Gly Cys Asn Gly Thr

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Phe	Pro	Gly	Ile	Pro	Gly
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Gln	Gly	Pro	Val	Gly	Pro
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Gly	Val	Pro	Gly	Gln	Ala
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 Ile Pro Leu Glu Lys Met Ser Val Ser Met Thr Met Asn Gly Ala Val
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 Phe Met Val Arg Asn Thr Tyr Ile Phe Pro Pro Glu Pro Ser Met Lys
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Tyr	Glu	Asp	Gly	Phe	Ser	Ile	Pro	Leu	Ala	Gly	Glu	Glu	Thr	Thr	Glu		
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		740						745					750				
Cys	Arg	Ile	Ile	Tyr	Arg	Pro	Val	Ala	Gly	Gly	Glu	Ser	Arg	Glu	Val		
		755					760					765					
Thr	Thr	Pro	Pro	Asn	Gln	Arg	Arg	Arg	Thr	Leu	Glu	Asn	Leu	Ile	Pro		
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 1125 1130 1135
 Pro Tyr Asp Asn Thr Val Val Leu Glu Glu Leu Arg Ala Gly Thr Thr
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 Tyr Lys Val Asn Val Phe Gly Met Phe Asp Gly Gly Glu Ser Ser Pro
 1155 1160 1165
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 Ile Leu Ser Ser Gly Met Glu Cys Leu Thr Arg Ala Glu Ala Asp Ile
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 1235 1240 1245
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 1300 1305 1310
 Gln Asp Asp Val Glu Ala Pro Ser Lys Lys Leu Lys Asp Glu Gly Val
 1315 1320 1325
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 1330 1335 1340
 Met Ile Ala Thr Asp Pro Asp Asp Thr His Asp Tyr Asn Val Ala Asp
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 Phe Glu Ser Leu Ser Arg Ile Val Asp Asp Leu Thr Ile Asn Leu Cys
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 1380 1385 1390
 Ile Ser Glu Arg Thr His Arg Ser Phe Arg Val Ser Trp Thr Pro Pro
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 Gly Lys Arg Gln Glu Phe Tyr Val Ser Arg Met Glu Thr Ser Thr Val
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 1445 1450 1455
 Val Val Glu Asp Glu Tyr Ser Glu Pro Leu Lys Gly Thr Glu Lys Thr
 1460 1465 1470
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 1475 1480 1485
 Thr Met His Val Gln Trp Gln Pro Val Gly Gly Ala Thr Gly Tyr Ile
 1490 1495 1500
 Leu Ser Tyr Lys Pro Val Lys Asp Thr Glu Pro Thr Arg Pro Lys Glu
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 Val Arg Leu Gly Pro Thr Val Asn Asp Met Gln Leu Thr Asp Leu Val

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 Thr Ser Glu Pro Val Thr Val Arg Glu Val Thr Leu Pro Leu Pro Arg
 1555 1560 1565
 Pro Gln Asp Leu Lys Leu Arg Asp Val Thr His Ser Thr Met Asn Val
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 1825 1830 1835 1840
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 1845 1850 1855
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 1860 1865 1870
 Gln Tyr Lys Leu Phe Tyr Ala Pro Ala Ala Gly Gly Pro Glu Glu Leu
 1875 1880 1885
 Val Pro Ile Pro Gly Asn Thr Asn Tyr Ala Ile Leu Arg Asn Leu Gln
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 1925 1930 1935
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 1940 1945 1950
 Arg Trp Asp Pro Ala Pro Gly Pro Val Leu Gln Tyr Arg Val Val Tyr
 1955 1960 1965
 Ser Pro Val Asp Gly Thr Arg Pro Ser Glu Ser Ile Val Val Pro Gly
 1970 1975 1980
 Asn Thr Arg Met Val His Leu Glu Arg Leu Ile Pro Asp Thr Leu Tyr
 1985 1990 1995 2000
 Ser Val Asn Leu Val Ala Leu Tyr Ser Asp Gly Glu Gly Asn Pro Ser
 2005 2010 2015

Pro Ala Gln Gly Arg Thr Leu Pro Arg Ser Gly Pro Arg Asn Leu Arg
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 2275 2280 2285
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 Lys Ala Asp Ile Val Phe Leu Thr Asp Ala Ser Trp Ser Ile Gly Asp
 2325 2330 2335
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 2355 2360 2365
 Ser Asp Glu Val Lys Ser Glu Phe Lys Leu Asn Thr Tyr Asn Asp Lys
 2370 2375 2380
 Ala Leu Ala Leu Gly Ala Leu Gln Asn Ile Arg Tyr Arg Gly Gly Asn
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 Trp Glu Ser Gly Met Arg Lys Asn Val Pro Lys Val Leu Val Val Val
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 Gln Gln Ser Gly Phe Ser Val Phe Val Val Gly Val Ala Asp Val Asp
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 2465 2470 2475 2480
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 2485 2490 2495
 Ile Thr Phe Val Cys Glu Thr Ala Thr Ser Ser Cys Pro Leu Ile Tyr

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Val Asn Gln Pro Thr Ala Asp Leu His Pro Asn Gly Leu Pro Pro Ser		
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Tyr Thr Ile Ile Leu Leu Phe Arg Leu Leu Pro Glu Thr Pro Ser Asp		
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Pro Phe Ala Ile Trp Gln Ile Thr Asp Arg Asp Tyr Lys Pro Gln Val		
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Asp Thr Arg Gly Glu Val Gln Thr Val Thr Phe Asp Thr Glu Glu Val		
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Lys Thr Leu Phe Tyr Gly Ser Phe His Lys Val His Ile Val Val Thr		
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Ser Lys Ser Val Lys Ile Tyr Ile Asp Cys Tyr Glu Ile Ile Glu Lys		
2660	2665	2670
Asp Ile Lys Glu Ala Gly Asn Ile Thr Thr Asp Gly Tyr Glu Ile Leu		
2675	2680	2685
Gly Lys Leu Leu Lys Gly Glu Arg Lys Ser Ala Ala Phe Gln Ile Gln		
2690	2695	2700
Ser Phe Asp Ile Val Cys Ser Pro Val Trp Thr Ser Arg Asp Arg Cys		
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Cys Asp Ile Pro Ser Arg Arg Asp Glu Gly Lys Cys Pro Ala Phe Pro		
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Asn Ser Cys Thr Cys Thr Gln Asp Ser Val Gly Pro Pro Gly Pro Pro		
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2755	2760	2765
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Gly Arg Pro Gly Pro Ser Gly Leu Lys Gly Glu Lys Gly Asp Arg Gly		
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Glu Gln Leu Ile Ser Gly Gln Met Asn Arg Phe Asn Gln Met Leu Asn		
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Gln Ile Pro Asn Asp Tyr Gln Ser Ser Arg Asn Gln Pro Gly Pro Pro		
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Pro Gly Gly Arg Pro Gly Phe Pro Gly Thr Pro Gly Met Gln Gly Pro		
2965	2970	2975
Pro Gly Glu Arg Gly Leu Pro Gly Glu Lys Gly Glu Arg Gly Thr Gly		
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 Ser Arg Thr Gly Pro Pro Gly Ser Thr Gly Ser Arg Gly Pro Pro Gly
 3010 3015 3020
 Pro Pro Gly Arg Pro Gly Asn Ser Gly Ile Gln Gly Pro Pro Gly Pro
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 Ser Ala Met Tyr Cys Asp Glu Leu Lys Leu Lys Ser Val Pro Met Val
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Pro Pro Gly Ile Lys Tyr Leu Tyr Leu Arg Asn Asn Gln Ile Asp His
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Ile Asp Glu Lys Ala Phe Glu Asn Val Thr Asp Leu Gln Trp Leu Ile
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Leu Asp His Asn Leu Leu Glu Asn Ser Lys Ile Lys Gly Arg Val Phe
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Ser Lys Leu Lys Gln Leu Lys Lys Leu His Ile Asn His Asn Asn Leu
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Thr Glu Ser Val Gly Pro Leu Pro Lys Ser Leu Glu Asp Leu Gln Leu
130 135 140
Thr His Asn Lys Ile Thr Lys Leu Gly Ser Phe Glu Gly Leu Val Asn
145 150 155 160
Leu Thr Phe Ile His Leu Gln His Asn Arg Leu Lys Glu Asp Ala Val
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Ser Ala Ala Phe Lys Gly Leu Lys Ser Leu Glu Tyr Leu Asp Leu Ser
180 185 190
Phe Asn Gln Ile Ala Arg Leu Pro Ser Gly Leu Pro Val Ser Leu Leu
195 200 205
Thr Leu Tyr Leu Asp Asn Asn Lys Ile Ser Asn Ile Pro Asp Glu Tyr
210 215 220
Phe Lys Arg Phe Asn Ala Leu Gln Tyr Leu Arg Leu Ser His Asn Glu
225 230 235 240
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Val Glu Leu Asp Leu Ser Tyr Asn Lys Leu Lys Asn Ile Pro Thr Val
260 265 270
Asn Glu Asn Leu Glu Asn Tyr Tyr Leu Glu Val Asn Gln Leu Glu Lys
275 280 285
Phe Asp Ile Lys Ser Phe Cys Lys Ile Leu Gly Pro Leu Ser Tyr Ser
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 <212> PRT
 <213> Homo sapiens

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Asp Arg Asp Val Trp Lys Pro Glu Pro Cys Arg Ile Cys Val Cys Asp
50 55 60
Asn Gly Lys Val Leu Cys Asp Asp Val Ile Cys Asp Glu Thr Lys Asn
65 70 75 80
Cys Pro Gly Ala Glu Val Pro Glu Gly Glu Cys Cys Pro Val Cys Pro
85 90 95
Asp Gly Ser Glu Ser Pro Thr Asp Gln Glu Thr Thr Gly Val Glu Gly
100 105 110
Pro Lys Gly Asp Thr Gly Pro Arg Gly Pro Arg Gly Pro Ala Gly Pro
115 120 125
Pro Gly Arg Asp Gly Ile Pro Gly Gln Pro Gly Leu Pro Gly Pro Pro
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 Pro Gly Ala Pro Gly Pro Gln Gly Phe Gln Gly Pro Pro Gly Glu Pro
 195 200 205
 Gly Glu Pro Gly Ala Ser Gly Pro Met Gly Pro Arg Gly Pro Pro Gly
 210 215 220
 Pro Pro Gly Lys Asn Gly Asp Asp Gly Glu Ala Gly Lys Pro Gly Arg
 225 230 235 240
 Pro Gly Glu Arg Gly Pro Pro Gly Pro Gln Gly Ala Arg Gly Leu Pro
 245 250 255
 Gly Thr Ala Gly Leu Pro Gly Met Lys Gly His Arg Gly Phe Ser Gly
 260 265 270
 Leu Asp Gly Ala Lys Gly Asp Ala Gly Pro Ala Gly Pro Lys Gly Glu
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 Pro Gly Ser Pro Gly Glu Asn Gly Ala Pro Gly Gln Met Gly Pro Arg
 290 295 300
 Gly Leu Pro Gly Glu Arg Gly Arg Pro Gly Ala Pro Gly Pro Ala Gly
 305 310 315 320
 Ala Arg Gly Asn Asp Gly Ala Thr Gly Ala Ala Gly Pro Pro Gly Pro
 325 330 335
 Thr Gly Pro Ala Gly Pro Pro Gly Phe Pro Gly Ala Val Gly Ala Lys
 340 345 350
 Gly Glu Ala Gly Pro Gln Gly Pro Arg Gly Ser Glu Gly Pro Gln Gly
 355 360 365
 Val Arg Gly Glu Pro Gly Pro Gly Pro Ala Gly Ala Ala Gly Pro
 370 375 380
 Ala Gly Asn Pro Gly Ala Asp Gly Gln Pro Gly Ala Lys Gly Ala Asn
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 405 410 415
 Pro Ser Gly Pro Gln Gly Pro Gly Gly Pro Pro Gly Pro Lys Gly Asn
 420 425 430
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 485 490 495
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 Gly Ser Pro Gly Pro Asp Gly Lys Thr Gly Pro Pro Gly Pro Ala Gly
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 Gln Asp Gly Arg Pro Gly Pro Pro Gly Pro Pro Gly Ala Arg Gly Gln
 565 570 575
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 Gly Lys Ala Gly Glu Arg Gly Val Pro Gly Pro Pro Gly Ala Val Gly
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Ser Gly Ala Arg	Gly Glu Arg Gly Phe Pro Gly Glu Arg	Gly Val Gln				
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Asn Asp Gly Ala	Lys Gly Asp Ala Gly Ala Pro Gly Ala Pro Gly	Ser				
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Gln Gly Ala Pro	Gly Leu Gln Gly Met Pro Gly Glu Arg Gly Ala Ala					
	725		730		735	
Gly Leu Pro Gly	Pro Lys Gly Asp Arg Gly Asp Ala Gly Pro Lys Gly					
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Ala Asp Gly Ser	Pro Gly Lys Asp Gly Val Arg Gly Leu Thr Gly Pro					
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Ile Gly Pro Pro	Gly Pro Ala Gly Ala Pro Gly Asp Lys Gly Glu Ser					
	770		775		780	
Gly Pro Ser Gly	Pro Ala Gly Pro Thr Gly Ala Arg Gly Ala Pro Gly					
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Asp Arg Gly Glu	Pro Gly Pro Pro Gly Pro Ala Gly Phe Ala Gly Pro					
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Pro Gly Ala Asp	Gly Gln Pro Gly Ala Lys Gly Glu Pro Gly Asp Ala					
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Gly Ala Lys Gly	Asp Ala Gly Pro Gly Pro Ala Gly Pro Ala Gly					
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Pro Pro Gly Pro	Ile Gly Asn Val Gly Ala Pro Gly Ala Lys Gly Ala					
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Arg Gly Ser Ala	Gly Pro Gly Ala Thr Gly Phe Pro Gly Ala Ala					
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Gly Arg Val Gly	Pro Pro Gly Pro Ser Gly Asn Ala Gly Pro Pro Gly					
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Thr Gly Pro Ala	Gly Arg Pro Gly Glu Val Gly Pro Pro Gly Pro Pro					
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Gly Pro Ala Gly	Glu Lys Gly Ser Pro Gly Ala Asp Gly Pro Ala Gly					
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Val Gly Leu Pro	Gly Gln Arg Gly Glu Arg Gly Phe Pro Gly Leu Pro					
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Gly Pro Ala Gly	Pro Val Gly Pro Val Gly Ala Arg Gly Pro Ala Gly					
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Pro Gln Gly Pro	Arg Gly Asp Lys Gly Glu Thr Gly Glu Gln Gly Asp					
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Arg Gly Ile Lys	Gly His Arg Gly Phe Ser Gly Leu Gln Gly Pro Pro					
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					1120	

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 1315 1320 1325
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 <211> 412
 <212> PRT
 <213> Homo sapiens

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35 40 45
Ser Lys Leu Arg Leu Thr Ser Pro Pro Glu Pro Thr Val Met Thr His
50 55 60
Val Pro Tyr Gln Val Leu Ala Leu Tyr Asn Ser Thr Arg Glu Leu Leu
65 70 75 80
Glu Glu Met His Gly Glu Arg Glu Glu Gly Cys Thr Gln Glu Asn Thr
85 90 95
Glu Ser Glu Tyr Tyr Ala Lys Glu Ile His Lys Phe Asp Met Ile Gln
100 105 110
Gly Leu Ala Glu His Asn Glu Leu Ala Val Cys Pro Lys Gly Ile Thr
115 120 125
Ser Lys Val Phe Arg Phe Asn Val Ser Ser Val Glu Lys Asn Arg Thr
130 135 140
Asn Leu Phe Arg Ala Glu Phe Arg Val Leu Arg Val Pro Asn Pro Ser
145 150 155 160
Ser Lys Arg Asn Glu Gln Arg Ile Glu Leu Phe Gln Ile Leu Arg Pro

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165 170 175
 Asp Glu His Ile Ala Lys Gln Arg Tyr Ile Gly Gly Lys Asn Leu Pro
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 195 200 205
 Arg Glu Trp Leu Leu Arg Arg Glu Ser Asn Leu Gly Leu Glu Ile Ser
 210 215 220
 Ile His Cys Pro Cys His Thr Phe Gln Pro Asn Gly Asp Ile Leu Glu
 225 230 235 240
 Asn Ile His Glu Val Met Glu Ile Lys Phe Lys Gly Val Asp Asn Glu
 245 250 255
 Asp Asp His Gly Arg Gly Asp Leu Gly Arg Leu Lys Lys Gln Lys Asp
 260 265 270
 His His Asn Pro His Leu Ile Leu Met Met Ile Pro Pro His Arg Leu
 275 280 285
 Asp Asn Pro Gly Gln Gly Gly Gln Arg Lys Lys Arg Ala Leu Asp Thr
 290 295 300
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 305 310 315 320
 Tyr Ile Asp Phe Arg Gln Asp Leu Gly Trp Lys Trp Val His Glu Pro
 325 330 335
 Lys Gly Tyr Tyr Ala Asn Phe Cys Ser Gly Pro Cys Pro Tyr Leu Arg
 340 345 350
 Ser Ala Asp Thr Thr His Ser Thr Val Leu Gly Leu Tyr Asn Thr Leu
 355 360 365
 Asn Pro Glu Ala Ser Ala Ser Pro Cys Cys Val Pro Gln Asp Leu Glu
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165 170 175
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 Thr Arg Gly Thr Ala Glu Trp Leu Ser Phe Asp Val Thr Asp Thr Val
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 Arg Glu Trp Leu Leu Arg Arg Glu Ser Asn Leu Gly Leu Glu Ile Ser
 210 215 220
 Ile His Cys Pro Cys His Thr Phe Gln Pro Asn Gly Asp Ile Leu Glu
 225 230 235 240
 Asn Ile His Glu Val Met Glu Ile Lys Phe Lys Gly Val Asp Asn Glu
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 Asp Asp His Gly Arg Gly Asp Leu Gly Arg Leu Lys Lys Gln Lys Asp
 260 265 270
 His His Asn Pro His Leu Ile Leu Met Met Ile Pro Pro His Arg Leu
 275 280 285
 Asp Asn Pro Gly Gln Gly Gly Gln Arg Lys Lys Arg Ala Leu Asp Thr
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 Tyr Ile Asp Phe Arg Gln Asp Leu Gly Trp Lys Trp Val His Glu Pro
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 Lys Gly Tyr Tyr Ala Asn Phe Cys Ser Gly Pro Cys Pro Tyr Leu Arg
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 Ser Ala Asp Thr Thr His Ser Thr Val Leu Gly Leu Tyr Asn Thr Leu
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<210> 264
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 <213> Homo sapiens

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<210> 265
 <211> 1366
 <212> PRT
 <213> Homo sapiens

<400> 265

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			20					25					30		
Gly	Pro	Ala	Gly	Asp	Arg	Gly	Pro	Arg	Gly	Glu	Arg	Gly	Pro	Pro	Gly
		35					40					45			
Pro	Pro	Gly	Arg	Asp	Gly	Glu	Asp	Gly	Pro	Thr	Gly	Pro	Pro	Gly	Pro
	50					55					60				
Pro	Gly	Pro	Pro	Gly	Pro	Pro	Gly	Leu	Gly	Gly	Asn	Phe	Ala	Ala	Gln
65					70				75						80
Tyr	Asp	Gly	Lys	Gly	Val	Gly	Leu	Gly	Pro	Gly	Pro	Met	Gly	Leu	Met
			85					90					95		
Gly	Pro	Arg	Gly	Pro	Pro	Gly	Ala	Ala	Gly	Ala	Pro	Gly	Pro	Gln	Gly
			100					105					110		
Phe	Gln	Gly	Pro	Ala	Gly	Glu	Pro	Gly	Glu	Pro	Gly	Gln	Thr	Gly	Pro
		115					120					125			
Ala	Gly	Ala	Arg	Gly	Pro	Ala	Gly	Pro	Pro	Gly	Lys	Ala	Gly	Glu	Asp
		130					135				140				
Gly	His	Pro	Gly	Lys	Pro	Gly	Arg	Pro	Gly	Glu	Arg	Gly	Val	Val	Gly
145					150					155					160
Pro	Gln	Gly	Ala	Arg	Gly	Phe	Pro	Gly	Thr	Pro	Gly	Leu	Pro	Gly	Phe
			165					170						175	
Lys	Gly	Ile	Arg	Gly	His	Asn	Gly	Leu	Asp	Gly	Leu	Lys	Gly	Gln	Pro
			180				185						190		
Gly	Ala	Pro	Gly	Val	Lys	Gly	Glu	Pro	Gly	Ala	Pro	Gly	Glu	Asn	Gly
		195					200					205			
Thr	Pro	Gly	Gln	Thr	Gly	Ala	Arg	Gly	Leu	Pro	Gly	Glu	Arg	Gly	Arg
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Val	Gly	Ala	Pro	Gly	Pro	Ala	Gly	Ala	Arg	Gly	Ser	Asp	Gly	Ser	Val
225					230					235					240
Gly	Pro	Val	Gly	Pro	Ala	Gly	Pro	Ile	Gly	Ser	Ala	Gly	Pro	Pro	Gly
			245					250					255		
Phe	Pro	Gly	Ala	Pro	Gly	Pro	Lys	Gly	Glu	Ile	Gly	Ala	Val	Gly	Asn
			260				265						270		
Ala	Gly	Pro	Ala	Gly	Pro	Ala	Gly	Pro	Arg	Gly	Glu	Val	Gly	Leu	Pro
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Gly	Leu	Ser	Gly	Pro	Val	Gly	Pro	Pro	Gly	Asn	Pro	Gly	Ala	Asn	Gly
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Leu	Thr	Gly	Ala	Lys	Gly	Ala	Ala	Gly	Leu	Pro	Gly	Val	Ala	Gly	Ala
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Pro	Gly	Leu	Pro	Gly	Pro	Arg	Gly	Ile	Pro	Gly	Pro	Val	Gly	Ala	Ala
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Ser	Lys	Gly	Glu	Ser	Gly	Asn	Lys	Gly	Glu	Pro	Gly	Ser	Ala	Gly	Pro
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Gln Gly Pro Pro Gly Pro Ser Gly Glu Glu Gly Lys Arg Gly Pro Asn
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 Gly Glu Ala Gly Ser Ala Gly Pro Pro Gly Pro Pro Gly Leu Arg Gly
 385 390 395 400
 Ser Pro Gly Ser Arg Gly Leu Pro Gly Ala Asp Gly Arg Ala Gly Val
 405 410 415
 Met Gly Pro Pro Gly Ser Arg Gly Ala Ser Gly Pro Ala Gly Val Arg
 420 425 430
 Gly Pro Asn Gly Asp Ala Gly Arg Pro Gly Glu Pro Gly Leu Met Gly
 435 440 445
 Pro Arg Gly Leu Pro Gly Ser Pro Gly Asn Ile Gly Pro Ala Gly Lys
 450 455 460
 Glu Gly Pro Val Gly Leu Pro Gly Ile Asp Gly Arg Pro Gly Pro Ile
 465 470 475 480
 Gly Pro Ala Gly Ala Arg Gly Glu Pro Gly Asn Ile Gly Phe Pro Gly
 485 490 495
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 515 520 525
 Gly Ala Gln Gly Pro Pro Gly Pro Gln Gly Val Gln Gly Gly Lys Gly
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 545 550 555 560
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 675 680 685
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 Ala Lys Gly Glu Arg Gly Ala Lys Gly Pro Lys Gly Glu Asn Gly Val
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 755 760 765
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 770 775 780
 Met Thr Gly Phe Pro Gly Ala Ala Gly Arg Thr Gly Pro Pro Gly Pro
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 Gly Leu Arg Gly Pro Arg Gly Asp Gln Gly Pro Val Gly Arg Thr Gly
 820 825 830
 Glu Val Gly Ala Val Gly Pro Pro Gly Phe Ala Gly Glu Lys Gly Pro
 835 840 845
 Ser Gly Glu Ala Gly Thr Ala Gly Pro Pro Gly Thr Pro Gly Pro Gln

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Glu Arg Gly Leu Pro Gly Val Ala Gly Ala Val Gly Glu Pro Gly Pro				
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Gly Ser Pro Gly Val Asn Gly Ala Pro Gly Glu Ala Gly Arg Asp Gly				
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Asn Pro Gly Asn Asp Gly Pro Pro Gly Arg Asp Gly Gln Pro Gly His				
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Lys Gly Glu Arg Gly Tyr Pro Gly Asn Ile Gly Pro Val Gly Ala Ala				
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Gly Ala Pro Gly Pro His Gly Pro Val Gly Pro Ala Gly Lys His Gly				
	965		970	975
Asn Arg Gly Glu Thr Gly Pro Ser Gly Pro Val Gly Pro Ala Gly Ala				
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Val Gly Pro Arg Gly Pro Ser Gly Pro Gln Gly Ile Arg Gly Asp Lys				
	995		1000	1005
Gly Glu Pro Gly Glu Lys Gly Pro Arg Gly Leu Pro Gly Leu Lys Gly				
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His Asn Gly Leu Gln Gly Leu Pro Gly Ile Ala Gly His His Gly Asp				
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Gln Gly Ala Pro Gly Ser Val Gly Pro Ala Gly Pro Arg Gly Pro Ala				
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Gly Pro Ser Gly Pro Ala Gly Lys Asp Gly Arg Thr Gly His Pro Gly				
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Thr Val Gly Pro Ala Gly Ile Arg Gly Pro Gln Gly His Gln Gly Pro				
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Ala Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Val Ser				
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Gly Gly Gly Tyr Asp Phe Gly Tyr Asp Gly Asp Phe Tyr Arg Ala Asp				
1105		1110		1120
Gln Pro Arg Ser Ala Pro Ser Leu Arg Pro Lys Asp Tyr Glu Val Asp				
	1125		1130	1135
Ala Thr Leu Lys Ser Leu Asn Asn Gln Ile Glu Thr Leu Leu Thr Pro				
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Glu Gly Ser Arg Lys Asn Pro Ala Arg Thr Cys Arg Asp Leu Arg Leu				
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Ser His Pro Glu Trp Ser Ser Gly Tyr Tyr Trp Ile Asp Pro Asn Gln				
	1170		1175	1180
Gly Cys Thr Met Asp Ala Ile Lys Val Tyr Cys Asp Phe Ser Thr Gly				
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Glu Thr Cys Ile Arg Ala Gln Pro Glu Asn Ile Pro Ala Lys Asn Trp				
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Tyr Arg Ser Ser Lys Asp Lys Lys His Val Trp Leu Gly Glu Thr Ile				
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Asn Ala Gly Ser Gln Phe Glu Tyr Asn Val Glu Gly Val Thr Ser Lys				
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Glu Met Ala Thr Gln Leu Ala Phe Met Arg Leu Leu Ala Asn Tyr Ala				
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Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Ile Ala Tyr Met Asp				
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Glu Glu Thr Gly Asn Leu Lys Lys Ala Val Ile Leu Gln Gly Ser Asn				
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Asp Val Glu Leu Val Ala Glu Gly Asn Ser Arg Phe Thr Tyr Thr Val				
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Leu Val Asp Gly Cys Ser Lys Lys Thr Asn Glu Trp Gly Lys Thr Ile				
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Ile Glu Tyr Lys Thr Asn Lys Pro Ser Arg Leu Pro Phe Leu Asp Ile				
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 Gly Pro Val Cys Phe Lys
 1365

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 <212> DNA
 <213> Homo sapiens

<400> 266
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 gacgaccgag atgaggccca gcccgaggtg atcgctctga gtcgcttga ccccgcgat 1740
 ctctccgtgc accgggagac cacgtggaag acacggctgc ggcggaactc ctacgggaac 1800
 tgcttctctg tgtgcggcat cctgtatgcc gtggacagct acaaccagca ggaaggccag 1860
 gtcgcctacg ctttcgacac gcacacgggc accgacgac gccccagct gccgttctc 1920
 aacgagcacg cctacaccac ccagatcgac tacaaccca aggagcgggt gctgtacgcc 1980
 tgggacaatg gccaccagct cacctacacc ctccacttcg tggctctga 2028

<210> 267
 <211> 675
 <212> PRT
 <213> Homo sapiens

<400> 267
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 Gly Lys Gly Asn Lys Glu Arg Phe Lys Gly Glu Tyr Gln Leu Thr Trp
 20 25 30
 Ala Leu Lys Ala Thr His Cys Leu Ala Ala Thr His Trp Ser Pro Ser
 35 40 45
 Cys Pro Pro Gln Gln Val Phe Gly Asp Leu Asp Gln Val Arg Met Thr
 50 55 60
 Ser Glu Gly Ser Asp Cys Arg Cys Lys Cys Ile Met Arg Pro Leu Ser

65					70					75				80	
Lys	Asp	Ala	Cys	Ser	Arg	Val	Arg	Ser	Gly	Arg	Ala	Arg	Val	Glu	Asp
				85					90					95	
Phe	Tyr	Thr	Val	Glu	Thr	Val	Ser	Ser	Gly	Thr	Asp	Cys	Arg	Cys	Ser
			100					105					110		
Cys	Thr	Ala	Pro	Pro	Ser	Ser	Leu	Asn	Pro	Cys	Glu	Asn	Glu	Trp	Lys
		115					120					125			
Met	Glu	Lys	Leu	Lys	Lys	Gln	Ala	Pro	Glu	Leu	Leu	Lys	Leu	Gln	Ser
	130					135					140				
Met	Val	Asp	Leu	Leu	Glu	Gly	Thr	Leu	Tyr	Ser	Met	Asp	Leu	Met	Lys
145					150					155					160
Val	His	Ala	Tyr	Val	His	Lys	Val	Ala	Ser	Gln	Met	Asn	Thr	Leu	Glu
			165						170					175	
Glu	Ser	Ile	Lys	Ala	Asn	Leu	Ser	Arg	Glu	Asn	Glu	Val	Val	Lys	Asp
		180						185					190		
Ser	Val	Arg	His	Leu	Ser	Glu	Gln	Leu	Arg	His	Tyr	Glu	Asn	His	Ser
	195					200						205			
Ala	Ile	Met	Leu	Gly	Ile	Lys	Lys	Glu	Leu	Ser	Arg	Leu	Gly	Leu	Gln
	210					215					220				
Leu	Leu	Gln	Lys	Asp	Ala	Ala	Ala	Ala	Pro	Ala	Thr	Pro	Ala	Thr	Gly
225				230						235					240
Thr	Gly	Ser	Lys	Ala	Gln	Asp	Thr	Ala	Arg	Gly	Lys	Gly	Lys	Asp	Ile
			245					250					255		
Ser	Lys	Tyr	Gly	Ser	Val	Gln	Lys	Ser	Phe	Ala	Asp	Arg	Gly	Leu	Pro
		260						265					270		
Lys	Pro	Pro	Lys	Glu	Lys	Leu	Leu	Gln	Val	Glu	Lys	Leu	Arg	Lys	Glu
	275					280						285			
Ser	Gly	Lys	Gly	Ser	Phe	Leu	Gln	Pro	Thr	Ala	Lys	Pro	Arg	Ala	Leu
	290				295					300					
Ala	Gln	Gln	Gln	Ala	Val	Ile	Arg	Gly	Phe	Thr	Tyr	Tyr	Lys	Ala	Gly
305				310					315						320
Lys	Gln	Glu	Val	Thr	Glu	Ala	Val	Ala	Asp	Asn	Thr	Leu	Gln	Gly	Thr
			325					330					335		
Ser	Trp	Leu	Glu	Gln	Leu	Pro	Pro	Lys	Val	Glu	Gly	Arg	Ser	Asn	Ser
		340						345					350		
Ala	Glu	Pro	Asn	Ser	Ala	Glu	Gln	Asp	Glu	Ala	Glu	Pro	Arg	Ser	Ser
	355					360						365			
Glu	Arg	Val	Asp	Leu	Ala	Ser	Gly	Thr	Pro	Thr	Ser	Ser	Ile	Pro	Ala
	370					375					380				
Thr	Thr	Thr	Ala	Thr	Thr	Thr	Pro	Thr	Pro	Thr	Thr	Ser	Leu	Leu	Pro
385					390					395					400
Thr	Glu	Pro	Pro	Ser	Gly	Pro	Glu	Val	Ser	Ser	Gln	Gly	Arg	Glu	Ala
			405					410					415		
Ser	Cys	Glu	Gly	Thr	Leu	Arg	Ala	Val	Asp	Pro	Pro	Val	Arg	His	His
		420						425					430		
Ser	Tyr	Gly	Arg	His	Glu	Gly	Ala	Trp	Met	Lys	Asp	Pro	Ala	Ala	Arg
	435						440				445				
Asp	Asp	Arg	Ile	Tyr	Val	Thr	Asn	Tyr	Tyr	Tyr	Gly	Asn	Ser	Leu	Val
	450					455					460				
Glu	Phe	Arg	Asn	Leu	Glu	Asn	Phe	Lys	Gln	Gly	Arg	Trp	Ser	Asn	Met
465				470					475						480
Tyr	Lys	Leu	Pro	Tyr	Asn	Trp	Ile	Gly	Thr	Gly	His	Val	Val	Tyr	Gln
			485					490					495		
Gly	Ala	Phe	Tyr	Tyr	Asn	Arg	Ala	Phe	Thr	Lys	Asn	Ile	Ile	Lys	Tyr
	500							505					510		
Asp	Leu	Arg	Gln	Arg	Phe	Val	Ala	Ser	Trp	Ala	Leu	Leu	Pro	Asp	Val
	515					520						525			
Val	Tyr	Glu	Asp	Thr	Thr	Pro	Trp	Lys	Trp	Arg	Gly	His	Ser	Asp	Ile
	530					535				540					
Asp	Phe	Ala	Val	Asp	Glu	Ser	Gly	Leu	Trp	Val	Ile	Tyr	Pro	Ala	Val
545					550					555					560

Asp Asp Arg Asp Glu Ala Gln Pro Glu Val Ile Val Leu Ser Arg Leu
 565 570 575
 Asp Pro Gly Asp Leu Ser Val His Arg Glu Thr Thr Trp Lys Thr Arg
 580 585 590
 Leu Arg Arg Asn Ser Tyr Gly Asn Cys Phe Leu Val Cys Gly Ile Leu
 595 600 605
 Tyr Ala Val Asp Thr Tyr Asn Gln Gln Glu Gly Gln Val Ala Tyr Ala
 610 615 620
 Phe Asp Thr His Thr Gly Thr Asp Ala Arg Pro Gln Leu Pro Phe Leu
 625 630 635 640
 Asn Glu His Ala Tyr Thr Thr Gln Ile Asp Tyr Asn Pro Lys Glu Arg
 645 650 655
 Val Leu Tyr Ala Trp Asp Asn Gly His Gln Leu Thr Tyr Thr Leu His
 660 665 670
 Phe Val Val
 675

<210> 268
 <211> 1909
 <212> DNA
 <213> Homo sapiens

<400> 268
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 tctactgtat gaattatgct ttaagtagaa tttagtgcca aggagaactt ggtgaaataa 180
 attattttta tttttttttt atcctttaca aagccatgga ttttatttgg ttgatgtgtg 240
 ctctgtacac aagccatttc aataggatgg agctgttaat tattttccaa agagtaatat 300
 acatgcaaaa gtttcaataa aaactgggcc attaacaaat aaattaataa actaataagc 360
 attcccttct aggtttttgc caaactgcct atccaataac aaatttgaga atcgttgaaa 420
 aagctagtta tttttcagag aatgattttt cattattgaa actgttctcc cttagcaggcc 480
 attttccctt tttcctggga gtttagcaag tttaggagag aatagtcattg aaaagaaagg 540
 gaagaaaggg gagaagggaa gaggttaaaa agtaagtgtc cagacctatg aacgtaatcc 600
 ctttgctaga aatatttaag agcagctcag cttgggtgaa actgagtttt gtcattctcc 660
 atatttgcag gaaggtattt tctgacttgc aatgcagcta gatgtaaaat tttattttat 720
 catcctagaa agccttgact agaaaaatga ataaattttg agggtttctt gtccatatct 780
 ggcttgcatg tgccagaaag cagagaatag aaaatgtaat ctccaacatc caagcatcga 840
 aaccaaggg gtaggcaatt ctatgtaggt tttggacatg aagtttgggt catcttgggt 900
 tatgtctggc caactgctat taaacctctc ttgcttatag tctcttcatt ctattagaca 960
 agcacgtatc gaacacttgc ttgcacaaag gctctttagt taacaattta gcagctactg 1020
 tttgtgttaa acacactttt caccaaatag gttctgaggg aaacgagagc aatgactatt 1080
 taaagaaagg ctttccagc atcacttaca catcccaaaa ctaaaaagat caactcttcc 1140
 aactgagaaa agactcctgg ctttgaatgg aaacttacag cagagagtca caggccacgg 1200
 caacaacaac gacaacaaca aacatttggg atattattct caactcacgt ttttaataata 1260
 catcttaatt atttttctag tagagaaact acaaatcagc ctcttcaaca tttatatata 1320
 gtttaataag cctcttgcaa gttacttggt ctctcacctg aggtattttt ttctcccca 1380
 ccttgccctt gttcctccct tcctctctct cctttgcaag aggaaatatt taacatattt 1440
 gggccaact tcaataatgt aataattaat acattaaaag catttaactt cctttctaga 1500
 aaaatgcaca ggctaaggca tagacaaaac aaagagaaat gctgagaaat ttgccactgg 1560
 agacaagcaa tctgaataaa tatttgccaa aagttctttt tatgtcatat agtgtcagga 1620
 tttgaaggag ctattttttt taatgttgca actagcaact catcttcgga agacacagcc 1680
 aggagaatga agtagaagtg aaaggtttat aaatccattt gtaagcattt atcccatata 1740
 ttttaaatc aagaaaaatt gtgtttatct ttagaatttt gtattcaata ctttatgtac 1800
 tatgtgactc atgcttctgg ataaataaag caccaaatat gtatctgtaa ccacaatcac 1860
 acatattata ttaaatatat atctatataa caaaaaaaa aaaaaaaa 1909

<210> 269
 <211> 83
 <212> PRT
 <213> Homo sapiens

<400> 269
 Met Tyr Gly Asn Ile Leu Cys Pro Thr Leu His Thr Leu Cys Thr Gln
 1 5 10 15
 Ile Leu Tyr Cys Met Asn Tyr Ala Leu Ser Arg Ile Gln Cys Gln Gly
 20 25 30
 Glu Leu Gly Glu Ile Asn Tyr Phe Asn Phe Phe Phe Ile Leu Tyr Lys
 35 40 45
 Ala Met Asp Phe Ile Trp Leu Met Cys Ala Leu Tyr Thr Ser His Phe
 50 55 60
 Asn Arg Met Glu Leu Leu Ile Ile Phe Gln Arg Val Ile Asp Met Gln
 65 70 75 80
 Lys Phe Gln

<210> 270
 <211> 1720
 <212> DNA
 <213> Homo sapiens

<400> 270
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 ctatgtcagt tgggtgtgtt ctgcttatgt tagggtaatt gggcacggcc tttgtgtaac 120
 tggtagaatat ctctgaacct gggcatgaaa cagagagatg tcctaactct gggtagagagg 180
 aatcctcatt tttctctgcc ctctcactgt ggcacccctaa gaaaaaagtt ttgggttcct 240
 gcagcatgaa ggagagctct gctcccagaa tttgggagct ccagatttct tccagggtgt 300
 ggaggcatca atatatcagt ctgggaaagg ggttcctggg ccactccagg agctgagttg 360
 ggtggaagggt gctgagagtg tgggtggggg ccacttctga gcacccatgt ggcacccact 420
 gctggtccct gtttgtggct gggcactcag gaaaaatgtt ttggtgctaa gagtaaaaag 480
 ccaaccaaca aacacatctc ttttttctgt ctattcactg gaaagtaaaa gcagtctggg 540
 cgcaggctgg ggaccagat ggaattcaaa cttatgcctg ctctcaagggt gctcacgggt 600
 gctgataaac agctggataa aatgaagagt ctatgagtga gggatgcaga gccagggaag 660
 gctggtggag tgatgccacc agcacagggt tatgagtttg cagctgcaa ggggccaagg 720
 gatgagctgg ggcctcctt cccaatggca tctccccctg gtctggaact gaagacactg 780
 agcaatggtc cccaagcccc aaggagatca gctccccctg gccagtgge cccaaccagg 840
 gaggggtgtg agaatgcctg ctctcctca gaggagcatg agaccattt ccagaacct 900
 gggaacacga gactgggcag ctcaccagt cccccgggg gtgtctctc actgccccga 960
 tcccagcggg atgatctgtc ccttcattca gaggaggggc cagccctgga gcccgtagc 1020
 cgcccgttgg attatggctt tgtttccgcc ctctgtttcc tggtagtggt gattcttctg 1080
 gtggtgacag catacgccat cccccgtgag gctcagtgca atccggacac agtgacagcg 1140
 cgggagatgg aacgactgga gatgtactac gcccgcctag gctccacct ggacaggtgc 1200
 atcatcgag gctcgggct gctcacgggt ggcggcatgc tcttgtcgggt gctgctcatg 1260
 gtctccctgt gcaagggcga gctgtaccgc cggaggacct tcgtccccgg caaggggtcc 1320
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 taagaactag cccaccttat ctggctgctt tagctccagt gctacaagggt ccacccctg 1500
 ctcccgcaca cctgaccctt gccaaagccc tgggggttta aactgagctc acatagggcc 1560
 ttgtggaaga agtactgggt gctggaggga gagctcgggg ccagcccat gcccacacg 1620
 ggcaagcagc ccactgatct gttttgtagc tgagggtttg catacggttt tgtttggagg 1680
 atggcttctg ctgctaataa tacaaaagtt tggaaaccgc 1720

<210> 271
 <211> 256
 <212> PRT
 <213> Homo sapiens

<400> 271
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 Asp Glu Leu Gly Pro Ser Phe Pro Met Ala Ser Pro Pro Gly Leu Glu
 20 25 30
 Leu Lys Thr Leu Ser Asn Gly Pro Gln Ala Pro Arg Arg Ser Ala Pro

35	40	45
Leu Gly Pro Val Ala Pro Thr Arg Glu Gly Val Glu Asn Ala Cys Phe		
50	55	60
Ser Ser Glu Glu His Glu Thr His Phe Gln Asn Pro Gly Asn Thr Arg		
65	70	75
Leu Gly Ser Ser Pro Ser Pro Pro Gly Gly Val Ser Ser Leu Pro Arg		
85	90	95
Ser Gln Arg Asp Asp Leu Ser Leu His Ser Glu Glu Gly Pro Ala Leu		
100	105	110
Glu Pro Val Ser Arg Pro Val Asp Tyr Gly Phe Val Ser Ala Leu Val		
115	120	125
Phe Leu Val Ser Gly Ile Leu Val Val Thr Ala Tyr Ala Ile Pro		
130	135	140
Arg Glu Ala Arg Val Asn Pro Asp Thr Val Thr Ala Arg Glu Met Glu		
145	150	155
Arg Leu Glu Met Tyr Tyr Ala Arg Leu Gly Ser His Leu Asp Arg Cys		
165	170	175
Ile Ile Ala Gly Leu Gly Leu Leu Thr Val Gly Gly Met Leu Leu Ser		
180	185	190
Val Leu Leu Met Val Ser Leu Cys Lys Gly Glu Leu Tyr Arg Arg Arg		
195	200	205
Thr Phe Val Pro Gly Lys Gly Ser Arg Lys Thr Tyr Gly Ser Ile Asn		
210	215	220
Leu Arg Met Arg Gln Leu Asn Gly Asp Gly Gly Gln Ala Leu Val Glu		
225	230	235
Asn Glu Val Val Gln Val Ser Glu Thr Ser His Thr Leu Gln Arg Ser		
245	250	255

<210> 272
 <211> 1111
 <212> DNA
 <213> Homo sapiens

<400> 272	
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acgccatcaa gaagaagatg cagatgtctga agctcgacaa ggagaacgcc ttggatcgag	120
ctgagcaggc ggaggccgac aagaaggcgg cggaagacag gagcaagcag ctggaagatg	180
agctggtgtc actgcaaaag aaactcaagg gcaccgaaga tgaactggac aaatactctg	240
aggctctcaa agatgcccag gagaagctgg agctggcaga gaaaaaggcc accgatgctg	300
aagccgacgt agcttctctg aacagacgca tccagctggt tgaggaagag ttggatcgtg	360
cccaggagcg tctggcaaca gctttgcaga agctggagga agctgagaag gcagcagatg	420
agagttagag aggcattgaaa gtcattgaga gtcgagccca aaaagatgaa gaaaaaatgg	480
aaattcagga gatccaactg aaagaggcca agcacattgc tgaagatgcc gaccgcaaat	540
acgaagaggt ggcccgttaag ctggtcatca ttgagagcga cctggaacgt gcagaggagc	600
gggctgagct ctcagaaggc aaatgtgccg agcttgaaga agaattgaaa actgtgacga	660
acaacttgaa gtcactggag gctcaggctg agaagtactc gcagaaggaa gacagatatg	720
aggaagagat caaggtcctt tccgacaagc tgaaggaggc tgagactcgg gctgagtttg	780
cggagaggtc agtaactaaa ttggagaaaa gcattgatga cttagaagac gagctgtacg	840
ctcagaaact gaagtacaaa gccatcagcg aggagctgga ccacgctctc aacgatatga	900
cttccatata agtttctttg cttcacttct cccaagactc cctcgtcgag ctggatgtcc	960
cacctctctg agctctgcat ttgtctattc tccagctgac cctggttctc tctcttagca	1020
tctgcctta gagccaggca cacactgtgc tttctattgt acagaagctc ttcggttcag	1080
tgtaaaataa acactgtgta agctaaaaaa a	1111

<210> 273
 <211> 284
 <212> PRT
 <213> Homo sapiens

<400> 273
 Met Asp Ala Ile Lys Lys Lys Met Gln Met Leu Lys Leu Asp Lys Glu

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Asn Ala Leu Asp Arg Ala Glu Gln Ala Glu Ala Asp Lys Lys Ala Ala			
20	25	30	
Glu Asp Arg Ser Lys Gln Leu Glu Asp Glu Leu Val Ser Leu Gln Lys			
35	40	45	
Lys Leu Lys Gly Thr Glu Asp Glu Leu Asp Lys Tyr Ser Glu Ala Leu			
50	55	60	
Lys Asp Ala Gln Glu Lys Leu Glu Leu Ala Glu Lys Lys Ala Thr Asp			
65	70	75	80
Ala Glu Ala Asp Val Ala Ser Leu Asn Arg Arg Ile Gln Leu Val Glu			
85	90	95	
Glu Glu Leu Asp Arg Ala Gln Glu Arg Leu Ala Thr Ala Leu Gln Lys			
100	105	110	
Leu Glu Glu Ala Glu Lys Ala Ala Asp Glu Ser Glu Arg Gly Met Lys			
115	120	125	
Val Ile Glu Ser Arg Ala Gln Lys Asp Glu Glu Lys Met Glu Ile Gln			
130	135	140	
Glu Ile Gln Leu Lys Glu Ala Lys His Ile Ala Glu Asp Ala Asp Arg			
145	150	155	160
Lys Tyr Glu Glu Val Ala Arg Lys Leu Val Ile Ile Glu Ser Asp Leu			
165	170	175	
Glu Arg Ala Glu Glu Arg Ala Glu Leu Ser Glu Gly Lys Cys Ala Glu			
180	185	190	
Leu Glu Glu Glu Leu Lys Thr Val Thr Asn Asn Leu Lys Ser Leu Glu			
195	200	205	
Ala Gln Ala Glu Lys Tyr Ser Gln Lys Glu Asp Arg Tyr Glu Glu Glu			
210	215	220	
Ile Lys Val Leu Ser Asp Lys Leu Lys Glu Ala Glu Thr Arg Ala Glu			
225	230	235	240
Phe Ala Glu Arg Ser Val Thr Lys Leu Glu Lys Ser Ile Asp Asp Leu			
245	250	255	
Glu Asp Glu Leu Tyr Ala Gln Lys Leu Lys Tyr Lys Ala Ile Ser Glu			
260	265	270	
Glu Leu Asp His Ala Leu Asn Asp Met Thr Ser Ile			
275	280		

<210> 274

<211> 2032

<212> DNA

<213> Homo sapiens

<400> 274

cacccccgag	ccgggacctg	gcctccgccc	cttgttgtcg	cgccccgccc	gcgagcccg	60
cccgccagtc	ccccgcggc	ggccaccatg	agcacaggcc	tgcggtacaa	gagcaagctg	120
gcgacccag	aggacaagca	ggacattgac	aagcagtacg	tgggcttcgc	cacactgccc	180
aaccaggtgc	accgcaagtc	ggtgaagaaa	ggctttgact	tcacactcat	ggtggctggg	240
gagtcaggcc	tggggaagtc	cacactggtc	cacagcctct	tcctgacaga	cttgtacaag	300
gaccggaagc	tgctcagtc	tgaggagcgc	atcagccaga	cggtagagat	tctaaaacac	360
acgggtggaca	ttgaggagaa	gggagtcaag	ctgaagctca	ccatcgtgga	cacgccggga	420
ttcggggacg	ctgtcaacaa	caccgagtc	tggaaagccca	tcaccgacta	tgtggaccag	480
cagtttgagc	agtacttccg	tgatgagagc	ggcctcaacc	gaaagaacat	ccaagacaac	540
cgagtgcact	gctgcctata	cttcactctc	cccttcgggc	atgggctgcg	gccagtggat	600
gtgggtttca	tgaaggcatt	gcatgagaag	gtcaacatcg	tgectctcat	cgccaaagct	660
gactgtcttg	tccccagtga	gatccggaag	ctgaaggagc	ggatccggga	ggagattgac	720
aagtttgga	tccatgtata	ccagttccct	gagtgtagct	cgaagagga	tgaggacttc	780
aagcagcagg	accgggaact	gaaggagagc	gcgccttcg	ccgttatagg	cagcaacacg	840
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gtggagaacc	aggcgattg	cgacttcgtg	aagctgcgca	acatgctcat	ccgcacgcat	960
atgcacgacc	tcaaggacgt	gacgtgcgac	gtgcactacg	agaactaccg	cgcgactgc	1020
atccagcaga	tgaccagcaa	actgacccag	gacagccgca	tggagagccc	catcccgatc	1080
ctgccgctgc	ccaccccgga	cgccgagact	gagaagctta	tcaggatgaa	ggatgaggaa	1140

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ctgaggcgca tgcaggagat gctgcagagg atgaagcagc agatgcagga ccagtgcgc 1200
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ctgttccga cccggagacg cggggccaca gccccagct gaccctaatt tattctcagc 1320
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gagtgtctgag accccatttt ctgtcgaggg gggccgagtc ttcccttacc cccagacgcc 1680
tagcgggcag gggtgggctg aatcaaagg gagccctcca gacataagga ggccagaggc 1740
tgcaaggagc ggggtcgtga ccgttacac cccttctcca cagcccgccc cgacctggag 1800
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ctccogatgt tccacccgc atgacctt cccgccacac gatgctccgt tttctccgt 1980
tgtgaatgcc gcgtcctgtc ctggtgacag gagaacaatg ttggtgaacy tc 2032

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<210> 275

<211> 369

<212> PRT

<213> Homo sapiens

<400> 275

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Met Ser Thr Gly Leu Arg Tyr Lys Ser Lys Leu Ala Thr Pro Glu Asp
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Lys Gln Asp Ile Asp Lys Gln Tyr Val Gly Phe Ala Thr Leu Pro Asn
20 25 30
Gln Val His Arg Lys Ser Val Lys Lys Gly Phe Asp Phe Thr Leu Met
35 40 45
Val Ala Gly Glu Ser Gly Leu Gly Lys Ser Thr Leu Val His Ser Leu
50 55 60
Phe Leu Thr Asp Leu Tyr Lys Asp Arg Lys Leu Leu Ser Ala Glu Glu
65 70 75 80
Arg Ile Ser Gln Thr Val Glu Ile Leu Lys His Thr Val Asp Ile Glu
85 90 95
Glu Lys Gly Val Lys Leu Lys Leu Thr Ile Val Asp Thr Pro Gly Phe
100 105 110
Gly Asp Ala Val Asn Asn Thr Glu Cys Trp Lys Pro Ile Thr Asp Tyr
115 120 125
Val Asp Gln Gln Phe Glu Gln Tyr Phe Arg Asp Glu Ser Gly Leu Asn
130 135 140
Arg Lys Asn Ile Gln Asp Asn Arg Val His Cys Cys Leu Tyr Phe Ile
145 150 155 160
Ser Pro Phe Gly His Gly Leu Arg Pro Val Asp Val Gly Phe Met Lys
165 170 175
Ala Leu His Glu Lys Val Asn Ile Val Pro Leu Ile Ala Lys Ala Asp
180 185 190
Cys Leu Val Pro Ser Glu Ile Arg Lys Leu Lys Glu Arg Ile Arg Glu
195 200 205
Glu Ile Asp Lys Phe Gly Ile His Val Tyr Gln Phe Pro Glu Cys Asp
210 215 220
Ser Asp Glu Asp Glu Asp Phe Lys Gln Gln Asp Arg Glu Leu Lys Glu
225 230 235 240
Ser Ala Pro Phe Ala Val Ile Gly Ser Asn Thr Val Val Glu Ala Lys
245 250 255
Gly Gln Arg Val Arg Gly Arg Leu Tyr Pro Trp Gly Ile Val Glu Val
260 265 270
Glu Asn Gln Ala His Cys Asp Phe Val Lys Leu Arg Asn Met Leu Ile
275 280 285
Arg Thr His Met His Asp Leu Lys Asp Val Thr Cys Asp Val His Tyr
290 295 300
Glu Asn Tyr Arg Ala His Cys Ile Gln Gln Met Thr Ser Lys Leu Thr

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305 310 315 320
 Gln Asp Ser Arg Met Glu Ser Pro Ile Pro Ile Leu Pro Leu Pro Thr
 325 330 335
 Pro Asp Ala Glu Thr Glu Lys Leu Ile Arg Met Lys Asp Glu Glu Leu
 340 345 350
 Arg Arg Met Gln Glu Met Leu Gln Arg Met Lys Gln Gln Met Gln Asp
 355 360 365
 Gln

<210> 276
 <211> 1344
 <212> DNA
 <213> Homo sapiens

<400> 276
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 ctggaaaggg aaaaaaggca gcattcacca catcccaatc ctgaatccaa gagtctaaga 120
 tagtccccca ctctatcttc aggccttagag gattagatta atctcctgga gggaagactc 180
 ttcttgaaa catttttttt tatctgcctg tagctattgg gataattcgg gaaatccaca 240
 gggacagttc aagtcattctt tgctctctac tttctgttgc actctcagcc ttgttctctt 300
 tttagaaact gcatggtaac tattatatag cttaaagaaga gcattctgac ctctgccctg 360
 ggacttctctg gatcctcctc ttcttataaa tacaagggca gagctgggtat cccggggagc 420
 caggaagcag tgagcccagg agtcctcggc cagccctgcc tgcccaccag gaggatgaag 480
 gtctccgtgg ctgccctctc ctgccctcatg cttgttgctg tccttggtatc ccaggcccag 540
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 gttctgaaca gctttcactt tgctgctgac tgctgcacct cctacatctc acaaagcatc 660
 ccgtgttcac tcatgaaaag ttattttgaa acgagcagcg agtgctccaa gccagggtgc 720
 atattcctca ccaagaaggg gcggcaagtc tgtgccaaac ccagtgggtcc gggagttcag 780
 gattgcatga aaaagctgaa gcctactca atataataat aaagagacaa aagaggccag 840
 ccaccacct ccaacacctc ctgagcctct gaagctccca ccaggccagc tctcctccca 900
 caacagcttc ccacagcatg aagatctcctg tggtgccat tcccttcttc ctctcatca 960
 ccctgcctc agggaccaag actgaatcct cctcacgggg accttaccac ccctcagagt 1020
 gctgcttcac ctacactacc tacaagatcc cgcgtcagcg gattatggat tactatgaga 1080
 ccaacagcca gtgctccaag cccggaattg tcttcatcac caaaaggggc cattccgtct 1140
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 tgaccacgaa ggggtggcga aggcacagct cagagacata aagagaagat gccaaagccc 1260
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 aattaaagac cactcatgct ctcc 1344

<210> 277
 <211> 93
 <212> PRT
 <213> Homo sapiens

<400> 277
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 Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
 20 25 30
 Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
 35 40 45
 Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
 50 55 60
 Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
 65 70 75 80
 Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
 85 90

<210> 278
 <211> 1344

<212> DNA

<213> Homo sapiens

<400> 278

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tagtccccc	ctcctatctc	aggcttagag	gattagatta	atctcctgga	gggaagactc	180
ttccttgaaa	catttttttt	tatctgectg	tagctattgg	gataattcgg	gaaatccaca	240
gggacagttc	aagtcactct	tgtcctctac	tttctgttgc	actctcagcc	ttgttctctt	300
tttagaaact	gcatggtaac	tattatatag	ctaaagaaga	gcattctgac	ctctgccctg	360
ggacttctctg	gacccctctc	ttcttataaa	tacaagggca	gagctgggat	cccggggagc	420
caggaagcag	tgagcccagg	agtccctggc	cagccctgcc	tgcccaccag	gaggatgaag	480
gtctccgtgg	ctgccctctc	ctgcctcatg	cttgttgcctg	tccttggatc	ccaggcccag	540
ttcacaaatg	atgcagagac	agagttaatg	atgtcaaagc	ttccactgga	aaatccagta	600
gttctgaaca	gctttcactt	tgtctgtgac	tgtctgcact	cctacatctc	acaaagcatc	660
ccgtgttcac	tcatgaaaag	ttattttgaa	acgagcagcg	agtgtcccaa	gccaggtgtc	720
atattcctca	ccaagaaggg	gcggcaagtc	tgtgccaaac	ccagtgggtcc	gggagttbag	780
gattgcatga	aaaagctgaa	gccctactca	atataataat	aaagagacaa	aagaggccag	840
ccaccacact	ccaacacctc	ctgagcctct	gaagctccca	ccaggccagc	tctcctccca	900
caacagcttc	ccacagcatg	aagatctccg	tggtctccat	tccttctctc	ctcctcatca	960
ccatcgccct	agggaccaag	actgaatcct	cctcacgggg	acettaccac	ccctcagagt	1020
gctgcttcac	ctacactacc	tacaagatcc	cgcgtcagcg	gattatggat	tactatgaga	1080
ccaacagcca	gtgctccaag	cccgggaattg	tcttcatcac	caaaaggggc	cattccgtct	1140
gtaccaaccc	cagtgacaag	tgggtccagg	actatatcaa	ggacatgaag	gagaactgag	1200
tgaccagaa	ggggtggcga	aggcacagct	cagagacata	aagagaagat	gccaaggccc	1260
cctcctccac	ccaccgctaa	ctctcagccc	cagtcaccct	cttggagctt	ccctgctttg	1320
aattaaagac	cactcatgct	cttc				1344

<210> 279

<211> 93

<212> PRT

<213> Homo sapiens

<400> 279

Met	Lys	Ile	Ser	Val	Ala	Ala	Ile	Pro	Phe	Phe	Leu	Leu	Ile	Thr	Ile
1				5					10				15		
Ala	Leu	Gly	Thr	Lys	Thr	Glu	Ser	Ser	Ser	Arg	Gly	Pro	Tyr	His	Pro
			20					25				30			
Ser	Glu	Cys	Cys	Phe	Thr	Tyr	Thr	Thr	Tyr	Lys	Ile	Pro	Arg	Gln	Arg
		35					40					45			
Ile	Met	Asp	Tyr	Tyr	Glu	Thr	Asn	Ser	Gln	Cys	Ser	Lys	Pro	Gly	Ile
	50					55					60				
Val	Phe	Ile	Thr	Lys	Arg	Gly	His	Ser	Val	Cys	Thr	Asn	Pro	Ser	Asp
65					70				75						80
Lys	Trp	Val	Gln	Asp	Tyr	Ile	Lys	Asp	Met	Lys	Glu	Asn			
			85					90							

<210> 280

<211> 1344

<212> DNA

<213> Homo sapiens

<400> 280

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tagtccccc	ctcctatctc	aggcttagag	gattagatta	atctcctgga	gggaagactc	180
ttccttgaaa	catttttttt	tatctgectg	tagctattgg	gataattcgg	gaaatccaca	240
gggacagttc	aagtcactct	tgtcctctac	tttctgttgc	actctcagcc	ttgttctctt	300
tttagaaact	gcatggtaac	tattatatag	ctaaagaaga	gcattctgac	ctctgccctg	360
ggacttctctg	gacccctctc	ttcttataaa	tacaagggca	gagctgggat	cccggggagc	420
caggaagcag	tgagcccagg	agtccctggc	cagccctgcc	tgcccaccag	gaggatgaag	480

gtctccgtgg	ctgccctctc	ctgcctcatg	cttggtgctg	tccttggatc	ccaggcccag	540
ttcacaaatg	atgcagagac	agagttaatg	atgtcaaagc	ttccactgga	aaatccagta	600
gttctgaaca	gctttcactt	tgctgtgac	tgctgcacct	cctacatctc	acaaagcatc	660
ccgtgttcac	tcatgaaaag	ttattttgaa	acgagcagcg	agtgtctcaa	gccagggtgc	720
atattcctca	ccaagaaggg	gcggcaagtc	tgtgccaaac	ccagtgggtcc	gggagttcag	780
gattgcatga	aaaagctgaa	gccctactca	atataataat	aaagagacaa	aagaggccag	840
ccacccacct	ccaacacctc	ctgagcctct	gaagctccca	ccaggccagc	tctcctccca	900
caacagcttc	ccacagcatg	aagatctccg	tggtgcat	tcccttcttc	ctcctcatca	960
ccatcgccct	agggaccaag	actgaatcct	cctcacgggg	accttaccac	ccctcagagt	1020
gctgtttcac	ctacactacc	tacaagatcc	cgcgtcagcg	gattatggat	tactatgaga	1080
ccaacagcca	gtgctccaag	cccgggaattg	tcttcacac	caaaaggggc	cattccgtct	1140
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tgaccagaa	ggggtggcga	aggcacagct	cagagacata	aagagaagat	gccaaggccc	1260
cctcctccac	ccaccgctaa	ctctcagccc	cagtcaccct	cttgagctt	ccctgctttg	1320
aattaaagac	cactcatgct	cttc				1344

<210> 281

<211> 93

<212> PRT

<213> Homo sapiens

<400> 281

Met	Lys	Ile	Ser	Val	Ala	Ala	Ile	Pro	Phe	Phe	Leu	Leu	Ile	Thr	Ile
1				5					10					15	
Ala	Leu	Gly	Thr	Lys	Thr	Glu	Ser	Ser	Arg	Gly	Pro	Tyr	His	Pro	
			20					25					30		
Ser	Glu	Cys	Cys	Phe	Thr	Tyr	Thr	Thr	Tyr	Lys	Ile	Pro	Arg	Gln	Arg
		35					40					45			
Ile	Met	Asp	Tyr	Tyr	Glu	Thr	Asn	Ser	Gln	Cys	Ser	Lys	Pro	Gly	Ile
	50					55					60				
Val	Phe	Ile	Thr	Lys	Arg	Gly	His	Ser	Val	Cys	Thr	Asn	Pro	Ser	Asp
65					70					75				80	
Lys	Trp	Val	Gln	Asp	Tyr	Ile	Lys	Asp	Met	Lys	Glu	Asn			
			85					90							

<210> 282

<211> 2750

<212> DNA

<213> Homo sapiens

<400> 282

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gagagaaaac	agttaaataa	aaactaattt	aatacaaaat	ttagctgggc	ttggtggcac	180
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cgtagattgc	agttagccaa	gatcatccca	ctgcactcca	gcctgggcga	cagagtgaga	300
cacagtctca	aacaaaaaaa	aacaaaaagg	aatttagagt	agcccatggg	gtagctatgc	360
ttaccaacat	ccagtgggat	ccccgtggat	tctccctacc	cctttttaag	aggattgttg	420
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atccagcttt	gcttggacct	gaccactaca	gtccagaagg	attgctttgt	agcggaaatg	540
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tctaccacag	atcctgtgat	gagccagtgt	gcatgtctgg	aggaagttca	cttaccaaac	660
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attactggaa	ccacagaaaa	ttctcctgca	gacagatctc	agaagattca	tgctggtgac	780
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tcacctccac	ccgcgacaac	ccagtcacct	gaaagcacta	tggtacacct	actgaagaag	1020
gagaagtcag	ccatcctgga	tctttatatt	cctcctccgc	ctgctgttcc	ctactctccc	1080
cgggatgaga	atggcagttt	tgtttatgga	gggtccagta	agtgcaaaca	accattgcct	1140
ggtcctaagg	gttcagagtc	ccgaattcc	ttcttgacc	aggaaagccg	gagacgaaga	1200

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ttaaactgaa tgtatgatat tttgttagaa tggaaaagta ctatcttgtt aatttaagta 2700
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<210> 283

<211> 380

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> (1)...(380)

<223> Xaa = Any Amino Acid

<400> 283

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 20          25          30
Cys Leu Glu Glu Val His Leu Pro Asn Ile Lys Pro Gly Glu Gly Leu
 35          40          45
Gly Met Tyr Ile Lys Ser Thr Tyr Asp Gly Leu His Val Ile Thr Gly
 50          55          60
Thr Thr Glu Asn Ser Pro Ala Asp Arg Ser Gln Lys Ile His Ala Gly
 65          70          75          80
Asp Glu Val Ile Gln Val Asn Gln Gln Thr Val Val Gly Trp Gln Leu
 85          90          95
Lys Asn Leu Val Lys Lys Leu Arg Glu Asn Pro Thr Gly Val Val Leu
100          105          110
Leu Leu Lys Lys Arg Pro Thr Gly Ser Phe Asn Phe Thr Pro Ala Pro
115          120          125
Leu Lys Asn Leu Arg Trp Lys Pro Pro Leu Val Gln Thr Ser Pro Pro
130          135          140
Pro Ala Thr Thr Gln Ser Pro Glu Ser Thr Met Asp Thr Ser Leu Lys
145          150          155          160
Lys Glu Lys Ser Ala Ile Leu Asp Leu Tyr Ile Pro Pro Pro Pro Ala
165          170          175
Val Pro Tyr Ser Pro Arg Asp Glu Asn Gly Ser Phe Val Tyr Gly Gly

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<210> 284
<211> 1789
<212> DNA
<213> Homo sapiens
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<400> 284						
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aatactacag	ttgagaagaa	gaggttaaac	gaaccattac	cagacaacag	tggaaaaaaa	960
aagccttacg	atctatgccc	aagtccagaa	accaggtcct	cttcagaaga	aacttgactc	1020
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<210> 285
 <211> 335
 <212> PRT
 <213> Homo sapiens

<400> 285
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 35 40 45
 Tyr Glu Arg Ile Asn Lys Ser Met Asn Lys Ser Ile His Ile Val Val
 50 55 60
 Thr Met Ala Lys Ser Leu Glu Asn Ser Val Glu Asn Lys Ile Val Ser
 65 70 75 80
 Leu Asp Pro Ser Glu Ala Gly Pro Pro Arg Tyr Leu Gly Asp Arg Tyr
 85 90 95
 Lys Phe Tyr Leu Glu Asn Leu Thr Leu Gly Ile Arg Glu Ser Arg Lys
 100 105 110
 Glu Asp Glu Gly Trp Tyr Leu Met Thr Leu Glu Lys Asn Val Ser Val
 115 120 125
 Gln Arg Phe Cys Leu Gln Leu Arg Leu Tyr Glu Gln Val Ser Thr Pro
 130 135 140
 Glu Ile Lys Val Leu Asn Lys Thr Gln Glu Asn Gly Thr Cys Thr Leu
 145 150 155 160
 Ile Leu Gly Cys Thr Val Glu Lys Gly Asp His Val Ala Tyr Ser Trp
 165 170 175
 Ser Glu Lys Ala Gly Thr His Pro Leu Asn Pro Ala Asn Ser Ser His
 180 185 190
 Leu Leu Ser Leu Thr Leu Gly Pro Gln His Ala Asp Asn Ile Tyr Ile
 195 200 205
 Cys Thr Val Ser Asn Pro Ile Ser Asn Asn Ser Gln Thr Phe Ser Pro
 210 215 220
 Trp Pro Gly Cys Arg Thr Asp Pro Ser Glu Thr Lys Pro Trp Ala Val
 225 230 235 240
 Tyr Ala Gly Leu Leu Gly Gly Val Ile Met Ile Leu Ile Met Val Val
 245 250 255
 Ile Leu Gln Leu Arg Arg Arg Gly Lys Thr Asn His Tyr Gln Thr Thr
 260 265 270
 Val Glu Lys Lys Ser Leu Thr Ile Tyr Ala Gln Val Gln Lys Pro Gly
 275 280 285
 Pro Leu Gln Lys Lys Leu Asp Ser Phe Pro Ala Gln Asp Pro Cys Thr
 290 295 300
 Thr Ile Tyr Val Ala Ala Thr Glu Pro Val Pro Glu Ser Val Gln Glu
 305 310 315 320
 Thr Asn Ser Ile Thr Val Tyr Ala Ser Val Thr Leu Pro Glu Ser
 325 330 335

<210> 286
 <211> 305
 <212> PRT
 <213> Homo sapiens

<400> 286
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 20 25 30

Pro Lys Ile Leu Arg Gln Leu Gly Ser Lys Val Leu Leu Pro Leu Thr
 35 40 45
 Tyr Glu Arg Ile Asn Lys Ser Met Asn Lys Ser Ile His Ile Val Val
 50 55 60
 Thr Met Ala Lys Ser Leu Glu Asn Ser Val Glu Asn Lys Ile Val Ser
 65 70 75 80
 Leu Asp Pro Ser Glu Ala Gly Pro Pro Arg Tyr Leu Gly Asp Arg Tyr
 85 90 95
 Lys Phe Tyr Leu Glu Asn Leu Thr Leu Gly Ile Arg Glu Ser Arg Lys
 100 105 110
 Glu Asp Glu Gly Trp Tyr Leu Met Thr Leu Glu Lys Asn Val Ser Val
 115 120 125
 Gln Arg Phe Cys Leu Gln Leu Arg Leu Tyr Glu Gln Val Ser Thr Pro
 130 135 140
 Glu Ile Lys Val Leu Asn Lys Thr Gln Glu Asn Gly Thr Cys Thr Leu
 145 150 155 160
 Ile Leu Gly Cys Thr Val Glu Lys Gly Asp His Val Ala Tyr Ser Trp
 165 170 175
 Ser Glu Lys Ala Gly Thr His Pro Leu Asn Pro Ala Asn Ser Ser His
 180 185 190
 Leu Leu Ser Leu Thr Leu Gly Pro Gln His Ala Asp Asn Ile Tyr Ile
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 Cys Thr Val Ser Asn Pro Ile Ser Asn Asn Ser Gln Thr Phe Ser Pro
 210 215 220
 Trp Pro Gly Cys Arg Thr Asp Pro Ser Gly Lys Thr Asn His Tyr Gln
 225 230 235 240
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 245 250 255
 Pro Gly Pro Leu Gln Lys Lys Leu Asp Ser Phe Pro Ala Gln Asp Pro
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 Cys Thr Thr Ile Tyr Val Ala Ala Thr Glu Pro Val Pro Glu Ser Val
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 Ser
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<210> 287
 <211> 298
 <212> PRT
 <213> Homo sapiens

<400> 287
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 35 40 45
 Tyr Glu Arg Ile Asn Lys Ser Met Asn Lys Ser Ile His Ile Val Val
 50 55 60
 Thr Met Ala Lys Ser Leu Glu Asn Ser Val Glu Asn Lys Ile Val Ser
 65 70 75 80
 Leu Asp Pro Ser Glu Ala Gly Pro Pro Arg Tyr Leu Gly Asp Arg Tyr
 85 90 95
 Lys Phe Tyr Leu Glu Asn Leu Thr Leu Gly Ile Arg Glu Ser Arg Lys
 100 105 110
 Glu Asp Glu Gly Trp Tyr Leu Met Thr Leu Glu Lys Asn Val Ser Val
 115 120 125
 Gln Arg Phe Cys Leu Gln Leu Arg Leu Tyr Glu Gln Val Ser Thr Pro
 130 135 140

Glu Ile Lys Val Leu Asn Lys Thr Gln Glu Asn Gly Thr Cys Thr Leu
 145 150 155 160
 Ile Leu Gly Cys Thr Val Glu Lys Gly Asp His Val Ala Tyr Ser Trp
 165 170 175
 Ser Glu Lys Ala Gly Thr His Pro Leu Asn Pro Ala Asn Ser Ser His
 180 185 190
 Leu Leu Ser Leu Thr Leu Gly Pro Gln His Ala Asp Asn Ile Tyr Ile
 195 200 205
 Cys Thr Val Ser Asn Pro Ile Ser Asn Asn Ser Gln Thr Phe Ser Pro
 210 215 220
 Trp Pro Gly Cys Arg Thr Asp Pro Ser Glu Thr Lys Pro Trp Ala Val
 225 230 235 240
 Tyr Ala Gly Leu Leu Gly Gly Val Ile Met Ile Leu Ile Met Val Val
 245 250 255
 Ile Leu Gln Leu Arg Arg Arg Gly Lys Thr Asn His Tyr Gln Thr Thr
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 Val Glu Lys Lys Ser Leu Thr Ile Tyr Ala Gln Val Gln Lys Pro Gly
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 <211> 3640
 <212> DNA
 <213> Homo sapiens

<400> 288
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<210> 289

<211> 628

<212> PRT

<213> Homo sapiens

<400> 289

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35 40 45
Ala Asp Thr Thr Cys Gly Gln Asn Ala Thr Glu Leu Tyr Cys Phe Tyr
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Ser Glu Asn Thr Asp Leu Thr Cys Arg Gln Pro Lys Cys Asp Lys Cys
65 70 75 80
Asn Ala Ala Tyr Pro His Leu Ala His Leu Pro Ser Ala Met Ala Asp
85 90 95
Ser Ser Phe Arg Phe Pro Arg Thr Trp Trp Gln Ser Ala Glu Asp Val
100 105 110
His Arg Glu Lys Ile Gln Leu Asp Leu Glu Ala Glu Phe Tyr Phe Thr
115 120 125
His Leu Ile Val Met Phe Lys Ser Pro Arg Pro Ala Ala Met Val Leu
130 135 140
Asp Arg Ser Gln Asp Phe Gly Lys Thr Trp Lys Pro Tyr Lys Tyr Phe
145 150 155 160
Ala Thr Asn Cys Ser Ala Thr Phe Gly Leu Glu Asp Asp Val Val Lys
165 170 175
Lys Gly Ala Ile Cys Thr Ser Lys Tyr Ser Ser Pro Phe Pro Cys Thr
180 185 190
Gly Gly Glu Val Ile Phe Lys Ala Leu Ser Pro Pro Tyr Asp Thr Glu
195 200 205
Asn Pro Tyr Ser Ala Lys Val Gln Glu Gln Leu Lys Ile Thr Asn Leu

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210	215	220
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Leu Asn Glu Glu Pro Gln His Phe Thr His Tyr Ala Ile Tyr Asp Phe		
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Ile Val Lys Gly Ser Cys Phe Cys Asn Gly His Ala Asp Gln Cys Ile		
	260	265
Pro Val His Gly Phe Arg Pro Val Lys Ala Pro Gly Thr Phe His Met		
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Val His Gly Lys Cys Met Cys Lys His Asn Thr Ala Gly Ser His Cys		
	290	295
Gln His Cys Ala Pro Leu Tyr Asn Asp Arg Pro Trp Glu Ala Ala Asp		
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Gly Lys Thr Gly Ala Pro Asn Glu Cys Arg Thr Cys Lys Cys Asn Gly		
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His Ala Asp Thr Cys His Phe Asp Val Asn Val Trp Glu Ala Ser Gly		
	340	345
Asn Arg Ser Gly Gly Val Cys Asp Asp Cys Gln His Asn Thr Glu Gly		
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Gln Tyr Cys Gln Arg Cys Lys Pro Gly Phe Tyr Arg Asp Leu Arg Arg		
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Pro Phe Ser Ala Pro Asp Ala Cys Lys Pro Cys Ser Cys His Pro Val		
385	390	395
Gly Ser Ala Val Leu Pro Ala Asn Ser Val Thr Phe Cys Asp Pro Ser		
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Asn Gly Asp Cys Pro Cys Lys Pro Gly Val Ala Gly Arg Arg Cys Asp		
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Arg Cys Met Val Gly Tyr Trp Gly Phe Gly Asp Tyr Gly Cys Arg Pro		
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Cys Asp Cys Ala Gly Ser Cys Asp Pro Ile Thr Gly Asp Cys Ile Ser		
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Ser His Thr Asp Ile Asp Trp Tyr His Glu Val Pro Asp Phe Arg Pro		
465	470	475
Val His Asn Lys Ser Glu Pro Ala Trp Glu Trp Glu Asp Ala Gln Gly		
	485	490
Phe Ser Ala Leu Leu His Ser Gly Lys Cys Glu Cys Lys Glu Gln Thr		
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Leu Gly Asn Ala Lys Ala Phe Cys Gly Met Lys Tyr Ser Tyr Val Leu		
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Lys Ile Lys Ile Leu Ser Ala His Asp Lys Gly Thr His Val Glu Val		
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Asn Val Lys Ile Lys Lys Val Leu Lys Ser Thr Lys Leu Lys Ile Phe		
545	550	555
Arg Gly Lys Arg Thr Leu Tyr Pro Glu Ser Trp Thr Asp Arg Gly Cys		
	565	570
Thr Cys Pro Ile Leu Asn Pro Gly Leu Glu Tyr Leu Val Ala Gly His		
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Glu Asp Ile Arg Thr Gly Lys Leu Ile Val Asn Met Lys Ser Phe Val		
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Gln His Trp Lys Pro Ser Leu Gly Arg Lys Val Met Asp Ile Leu Lys		
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<210> 290
 <211> 2540
 <212> DNA
 <213> Mouse

<400> 290
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60


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<210> 291

<211> 765

<212> PRT

<213> Mouse

<400> 291

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Ser Cys Tyr Ala Leu Phe Pro Arg Arg Arg Thr Phe Leu Glu Ala Trp
35     40     45
Arg Ala Cys Arg Glu Leu Gly Gly Asn Leu Ala Thr Pro Arg Thr Pro
50     55     60
Glu Glu Ala Gln Arg Val Asp Ser Leu Val Gly Val Gly Pro Ala Asn
65     70     75     80
Gly Leu Leu Trp Ile Gly Leu Gln Arg Gln Ala Arg Gln Cys Gln Pro
85     90     95

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 Ala Phe Thr Asn Trp Ala Gln Pro Ala Thr Glu Gly Pro Cys Pro Ala
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 Gln Arg Cys Ala Ala Leu Glu Ala Ser Gly Glu His Arg Trp Leu Glu
 130 135 140
 Gly Ser Cys Thr Leu Ala Val Asp Gly Tyr Leu Cys Gln Phe Gly Phe
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 Glu Gly Ala Cys Pro Ala Leu Pro Leu Glu Val Gly Gln Ala Gly Pro
 165 170 175
 Ala Val Tyr Thr Thr Pro Phe Asn Leu Val Ser Ser Glu Phe Glu Trp
 180 185 190
 Leu Pro Phe Gly Ser Val Ala Ala Val Gln Cys Gln Ala Gly Arg Gly
 195 200 205
 Ala Ser Leu Leu Cys Val Lys Gln Pro Ser Gly Gly Val Gly Trp Ser
 210 215 220
 Gln Thr Gly Pro Leu Cys Pro Gly Thr Gly Cys Gly Pro Asp Asn Gly
 225 230 235 240
 Gly Cys Glu His Glu Cys Val Glu Glu Val Asp Gly Ala Val Ser Cys
 245 250 255
 Arg Cys Ser Glu Gly Phe Arg Leu Ala Ala Asp Gly His Ser Cys Glu
 260 265 270
 Asp Pro Cys Ala Gln Ala Pro Cys Glu Gln Gln Cys Glu Pro Gly Gly
 275 280 285
 Pro Gln Gly Tyr Ser Cys His Cys Arg Leu Gly Phe Arg Pro Ala Glu
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 Asp Asp Pro His Arg Cys Val Asp Thr Asp Glu Cys Gln Ile Ala Gly
 305 310 315 320
 Val Cys Gln Gln Met Cys Val Asn Tyr Val Gly Gly Phe Glu Cys Tyr
 325 330 335
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 340 345 350
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 355 360 365
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 Phe Asp Gly Thr Trp Thr Glu Glu Gln Gly Ile Leu Trp Leu Ala Pro
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 405 410 415
 Asp Gly Glu Pro Gln Arg Leu His Leu Glu Pro Thr Trp Pro Pro Pro
 420 425 430
 Leu Ser Ala Pro Arg Gly Pro Tyr His Ser Ser Val Val Ser Ala Thr
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 Arg Pro Met Val Ile Ser Ala Thr Arg Pro Thr Leu Pro Ser Ala His
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 515 520 525
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 Gln Ala Pro Met Ser Pro Asp Thr His Thr Ile Thr Tyr Leu Pro Pro
 545 550 555 560
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 565 570 575
 His Pro Leu Leu Pro Asp Ala Pro Gly Ile Arg Thr Gln Ala Pro Gln

580	585	590
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Ser Val His Glu Thr Pro Val Pro Ala Ala Asn Gln Pro Pro Ala Phe		
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Pro Ser Ser Pro Leu Pro Pro Gln Arg Pro Thr Asn Gln Thr Ser Ser		
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Ile Ser Pro Thr His Ser Tyr Ser Arg Ala Pro Leu Val Pro Arg Glu		
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Gly Val Pro Ser Pro Lys Ser Val Pro Gln Leu Pro Ser Val Pro Ser		
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Thr Ala Ala Pro Thr Ala Leu Ala Glu Ser Gly Leu Ala Gly Gln Ser		
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Gln Arg Asp Asp Arg Trp Leu Leu Val Ala Leu Leu Val Pro Thr Cys		
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Val Phe Leu Val Val Leu Leu Ala Leu Gly Ile Val Tyr Cys Thr Arg		
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Cys Gly Ser His Ala Pro Asn Lys Arg Ile Thr Asp Cys Tyr Arg Trp		
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 <212> DNA
 <213> Mouse

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 <212> PRT
 <213> Mouse

<400> 293

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Thr Pro Thr Ile Glu Asp Phe His Arg Lys Val Tyr Asn Ile His Gly
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65     70     75     80
Pro Ala Met Arg Arg Leu Ser Ile Leu Thr Gly Asp Val Phe Ile Leu
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Val Phe Ser Leu Asp Ser Arg Glu Ser Phe Asp Glu Val Lys Arg Leu
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Gln Lys Gln Ile Leu Glu Val Lys Ser Cys Leu Lys Asn Lys Thr Lys
115    120    125
Glu Ala Ala Glu Leu Pro Met Val Ile Cys Gly Asn Lys Asn Asp His
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Ser Glu Leu Cys Arg Gln Val Pro Ala Met Glu Ala Glu Leu Leu Val
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Ser Gly Asp Glu Asn Cys Ala Tyr Phe Glu Val Ser Ala Lys Lys Asn
165    170    175
Thr Asn Val Asn Glu Met Phe Tyr Val Leu Phe Ser Met Ala Lys Leu
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Pro His Glu Met Ser Pro Ala Leu His His Lys Ile Ser Val Gln Tyr
195    200    205
Gly Asp Ala Phe His Pro Arg Pro Phe Cys Met Arg Arg Thr Lys Val
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<400> 295

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Pro	Ile	Arg	Gly	Cys	Lys	Cys	Ser	Gly	Glu	Arg	Pro	Lys	Gly	Leu
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Phe	Leu	Gly	Leu	Ser	Leu	Leu	Glu	Lys	Leu	Asp	Leu	Arg	Ser	Asn
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Arg	Leu	Asp	Leu	Ser	Asn	Asn	Arg	Ile	Gly	Cys	Leu	Thr	Ser	Glu	Thr					
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Phe	Gln	Gly	Leu	Pro	Arg	Leu	Leu	Arg	Leu	Asn	Ile	Ser	Gly	Asn	Ile					
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Thr	Leu	Cys	Ala	Tyr	Pro	Ser	Ala	Leu	His	Ala	His	Ala	Leu	Ser	Ser					
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 610 615 620
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 Ile Phe Ala Gly Thr Ser Gly Cys Gly Val Gly Asn Leu Thr Glu Pro
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 Val Ala Val Ser Leu Arg His Trp Ala Glu Gly Ala Asp Pro Met Ala
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<212> PRT

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Ser Gln Asp Leu Gly Gly Ser Leu Ala Ile Asp Thr Leu Pro Asp
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Val Tyr Gly Pro Gly Glu Lys Gln Ser Gln Asp Leu Trp Val Asp Leu
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Tyr Gly His Pro Leu Arg Gln Ile Thr Ile Ala Thr Gly Gly Phe Ile
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Phe Met Gly Asp Met Leu His Arg Met Leu Thr Ala Thr Gln Tyr Val
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Ala Pro Leu Met Ala Asn Phe Asn Pro Gly Tyr Ser Asp Asn Ser Thr
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Ser Lys Ile Thr Thr Thr	Ser Ala Val Glu Phe	Thr Pro Leu Pro Thr
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Phe Asn Cys Ser Trp Cys	His Val Leu Gln Arg	Cys Ser Ser Gly Phe
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Glu Gly Lys Thr Cys Glu	Asp Phe Gln Asp Asp	Ser His Tyr Ser Ala
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Ser Lys Gly Pro Pro Val	His Leu Gly Thr Ile	Val Gly Ile Val Leu
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Gly His Pro Asn Ser Asn	Ala Ala Leu Phe Phe	Ile Glu Arg Arg Pro
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<210> 301
 <211> 562
 <212> PRT
 <213> Mouse

<400> 301
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 20 25 30
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 35 40 45
 Lys Ser Gly Ser Val Leu His His Trp Asn Glu Ile Tyr Tyr Phe Val
 50 55 60
 Glu Gln Leu Ala His Arg Phe Ile Ser Pro Gln Leu Arg Met Ser Phe
 65 70 75 80
 Ile Val Phe Ser Thr Arg Gly Thr Thr Leu Met Lys Leu Thr Glu Asp
 85 90 95
 Arg Glu Gln Ile Arg Gln Gly Leu Glu Leu Gln Lys Val Leu Pro
 100 105 110
 Gly Gly Asp Thr Tyr Met His Glu Gly Phe Glu Arg Ala Ser Glu Gln
 115 120 125
 Ile Tyr Tyr Glu Asn Ser Gln Gly Tyr Arg Thr Ala Ser Val Ile Ile
 130 135 140
 Ala Leu Thr Asp Gly Glu Leu His Glu Asp Leu Phe Phe Tyr Ser Glu
 145 150 155 160
 Arg Glu Ala Asn Arg Ser Arg Asp Leu Gly Ala Ile Val Tyr Cys Val
 165 170 175
 Gly Val Lys Asp Phe Asn Glu Thr Gln Leu Ala Arg Ile Ala Asp Ser
 180 185 190
 Lys Asp His Val Phe Pro Val Asn Asp Gly Phe Gln Ala Leu Gln Gly
 195 200 205
 Ile Ile His Ser Ile Leu Lys Lys Ser Cys Ile Glu Ile Leu Ala Ala
 210 215 220
 Glu Pro Ser Thr Ile Cys Ala Gly Glu Ser Phe Gln Val Val Val Arg
 225 230 235 240
 Gly Asn Gly Phe Arg His Ala Arg Asn Val Asp Arg Val Leu Cys Ser
 245 250 255
 Phe Lys Ile Asn Asp Ser Val Thr Leu Asn Glu Lys Pro Phe Ala Val
 260 265 270
 Glu Asp Thr Tyr Leu Leu Cys Pro Ala Pro Ile Leu Lys Glu Val Gly
 275 280 285
 Met Lys Ala Ala Leu Gln Val Ser Met Asn Asp Gly Leu Ser Phe Ile
 290 295 300
 Ser Ser Ser Val Ile Ile Thr Thr Thr His Cys Ser Asp Gly Ser Ile
 305 310 315 320
 Leu Ala Ile Ala Leu Leu Val Leu Phe Leu Leu Leu Ala Leu Ala Leu
 325 330 335
 Leu Trp Trp Phe Trp Pro Leu Cys Cys Thr Val Ile Ile Lys Glu Val
 340 345 350
 Pro Pro Pro Pro Val Glu Glu Ser Glu Glu Glu Asp Asp Asp Gly Leu
 355 360 365
 Pro Lys Lys Lys Trp Pro Thr Val Asp Ala Ser Tyr Tyr Gly Gly Arg
 370 375 380

Gly Val Gly Gly Ile Lys Arg Met Glu Val Arg Trp Gly Glu Lys Gly
 385 390 395 400
 Ser Thr Glu Glu Gly Ala Lys Leu Glu Lys Ala Lys Asn Ala Arg Val
 405 410 415
 Lys Met Pro Glu Gln Glu Tyr Glu Phe Pro Glu Pro Arg Asn Leu Asn
 420 425 430
 Asn Asn Met Arg Arg Pro Ser Ser Pro Arg Lys Trp Tyr Ser Pro Ile
 435 440 445
 Lys Gly Lys Leu Asp Ala Leu Trp Val Leu Leu Arg Lys Gly Tyr Asp
 450 455 460
 Arg Val Ser Val Met Arg Pro Gln Pro Gly Asp Thr Gly Arg Cys Ile
 465 470 475 480
 Asn Phe Thr Arg Val Lys Asn Ser Gln Pro Ala Lys Tyr Pro Leu Asn
 485 490 495
 Asn Thr Tyr His Pro Ser Ser Pro Pro Ala Pro Ile Tyr Thr Pro
 500 505 510
 Pro Pro Pro Ala Pro His Cys Pro Pro Pro Ala Pro Ser Ala Pro Thr
 515 520 525
 Pro Pro Ile Pro Ser Pro Pro Ser Thr Leu Pro Pro Pro Pro Gln Ala
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 545 550 555 560
 Ser Val

<210> 302
 <211> 2690
 <212> DNA
 <213> Mouse

<400> 302
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<210> 303
 <211> 162
 <212> PRT
 <213> Mouse

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Asn Leu Arg Leu Asp Cys Arg His Glu Asn Asn Thr Lys Asp Asn Ser
          35          40          45
Ile Gln His Glu Phe Ser Leu Thr Arg Glu Lys Arg Lys His Val Leu
          50          55          60
Ser Gly Thr Leu Gly Ile Pro Glu His Thr Tyr Arg Ser Arg Val Thr
          65          70          75          80
Leu Ser Asn Gln Pro Tyr Ile Lys Val Leu Thr Leu Ala Asn Phe Thr
          85          90          95
Thr Lys Asp Glu Gly Asp Tyr Phe Cys Glu Leu Gln Val Ser Gly Ala
          100          105          110
Asn Pro Met Ser Ser Asn Lys Ser Ile Ser Val Tyr Arg Asp Lys Leu
          115          120          125
Val Lys Cys Gly Gly Ile Ser Leu Leu Val Gln Asn Thr Ser Trp Met
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Leu Leu Leu Leu Leu Ser Leu Ser Leu Leu Gln Ala Leu Asp Phe Ile
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Ser Leu

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<210> 304
 <211> 4588
 <212> DNA
 <213> Mouse

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<210> 305

<211> 1479

<212> PRT

<213> Mouse

<400> 305

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Ser Ala Ala Ala Leu Leu Glu Pro Asp Val Phe Leu Ile Phe Ser Gln
35      40      45
Gly Met Gln Gly Cys Leu Glu Ala Gln Gly Val Gln Val Arg Val Thr
50      55      60
Pro Phe Cys Asn Ala Ser Leu Pro Ala Gln Arg Trp Lys Trp Val Ser
65      70      75      80
Arg Asn Arg Leu Phe Asn Leu Gly Ala Thr Gln Cys Leu Gly Thr Gly
85      90      95
Trp Pro Val Thr Asn Thr Thr Val Ser Leu Gly Met Tyr Glu Cys Asp
100     105     110
Arg Glu Ala Leu Ser Leu Arg Met Ala Val Ser Tyr Thr Arg Gly Pro
115     120     125
Val Val Pro Ala Ser Gly Gly Ser Cys Lys Gln Cys Ile Gln Ala Trp
130     135     140
His Leu Glu Arg Gly Asp Gln Thr Arg Ser Gly His Trp Asn Ile Tyr
145     150     155     160
Gly Ser Glu Glu Asp Leu Cys Ala Arg Pro Tyr Tyr Glu Val Tyr Thr
165     170     175
Ile Gln Gly Asn Ser His Gly Lys Pro Cys Thr Ile Pro Phe Lys Tyr
180     185     190
Asp Asn Gln Trp Phe His Gly Cys Thr Ser Thr Gly Arg Glu Asp Gly
195     200     205
His Leu Trp Cys Ala Thr Thr Gln Asp Tyr Gly Lys Asp Glu Arg Trp
210     215     220
Gly Phe Cys Pro Ile Lys Ser Asn Asp Cys Glu Thr Phe Trp Asp Lys
225     230     235     240
Asp Gln Leu Thr Asp Ser Cys Tyr Gln Phe Asn Phe Gln Ser Thr Leu
245     250     255
Ser Trp Arg Glu Ala Trp Ala Ser Cys Glu Gln Gln Gly Ala Asp Leu
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Leu Ser Ile Thr Glu Ile His Glu Gln Thr Tyr Ile Asn Gly Leu Leu
275     280     285
Thr Gly Tyr Ser Ser Thr Leu Trp Ile Gly Leu Asn Asp Leu Asp Thr
290     295     300
Ser Gly Gly Trp Gln Trp Ser Asp Asn Ser Pro Leu Lys Tyr Leu Asn
305     310     315     320
Trp Glu Ser Asp Gln Pro Asp Asn Pro Gly Glu Glu Asn Cys Gly Val
325     330     335
Ile Arg Thr Glu Ser Ser Gly Gly Trp Gln Asn His Asp Cys Ser Ile
340     345     350
Ala Leu Pro Tyr Val Cys Lys Lys Lys Pro Asn Ala Thr Val Glu Pro
355     360     365
Ile Gln Pro Asp Arg Trp Thr Asn Val Lys Val Glu Cys Asp Pro Ser
370     375     380

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 Lys Gln Glu Val Glu Glu Leu Trp Ile Gly Leu Asn Asp Leu Lys Leu
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 Gln Met Asn Phe Glu Trp Ser Asp Gly Ser Leu Val Ser Phe Thr His
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 Trp His Pro Phe Glu Pro Asn Asn Phe Arg Asp Ser Leu Glu Asp Cys
 465 470 475 480
 Val Thr Ile Trp Gly Pro Glu Gly Arg Trp Asn Asp Ser Pro Cys Asn
 485 490 495
 Gln Ser Leu Pro Ser Ile Cys Lys Lys Ala Gly Arg Leu Ser Gln Gly
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 Ala Ala Glu Glu Asp His Asp Cys Arg Lys Gly Trp Thr Trp His Ser
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 Pro Ser Cys Tyr Trp Leu Gly Glu Asp Gln Val Ile Tyr Ser Asp Ala
 530 535 540
 Arg Arg Leu Cys Thr Asp His Gly Ser Gln Leu Val Thr Ile Thr Asn
 545 550 555 560
 Arg Phe Glu Gln Ala Phe Val Ser Ser Leu Ile Tyr Asn Trp Glu Gly
 565 570 575
 Glu Tyr Phe Trp Thr Ala Leu Gln Asp Leu Asn Ser Thr Gly Ser Phe
 580 585 590
 Arg Trp Leu Ser Gly Asp Glu Val Ile Tyr Thr His Trp Asn Arg Asp
 595 600 605
 Gln Pro Gly Tyr Arg Arg Gly Gly Cys Val Ala Leu Ala Thr Gly Ser
 610 615 620
 Ala Met Gly Leu Trp Glu Val Lys Asn Cys Thr Ser Phe Arg Ala Arg
 625 630 635 640
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 Gly Pro Asp Pro Thr Pro Ser Leu Thr Gly Ser Cys Pro Gln Gly Trp
 660 665 670
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 675 680 685
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 690 695 700
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 Phe Val Ala His Met Leu Asn Lys Ile Phe Gly Glu Ser Glu Pro Glu
 725 730 735
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 Arg Glu Gly His Ser Trp Arg Trp Ser Asp Gly Leu Gly Phe Ser Tyr
 755 760 765
 His Asn Phe Ala Arg Ser Arg His Asp Asp Asp Ile Arg Gly Cys
 770 775 780
 Ala Val Leu Asp Leu Ala Ser Leu Gln Trp Val Pro Met Gln Cys Gln
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 Thr Gln Leu Asp Trp Ile Cys Lys Ile Pro Arg Gly Val Asp Val Arg
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 Glu Ala Glu Tyr Lys Phe Phe Glu His His Ser Ser Trp Ala Gln Ala
 835 840 845
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 850 855 860
 Gln Ala Glu Leu Gly Phe Leu Gly Gln Asn Leu Gln Lys Leu Ser Ser

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 1 5 10 15
 Ile Gln Cys Ser Phe Tyr Arg Asp Lys Arg Ser Asn Ser Ser Gly Trp
 20 25 30
 Val Trp Trp Leu Met Pro Val Ile Pro Thr Leu Trp Glu Ala Lys Ala
 35 40 45
 Gly Gly Ser His Glu Val Arg Ser Ser Arg Pro Ala Trp Pro Thr Trp
 50 55 60
 Gln Asn Cys Leu Tyr
 65

PEM's
complete with table # 25 (PEM3) + # 47 (PEM6) are G1, rest are G3

Table 1. Previously characterized and novel Pan Endothelial Markers. The most abundant tags derived by summing the tags from Normal EC (N-EC's) and Tumor EC (T-EC's) SAGE libraries are listed in descending order. N-EC and T-EC SAGE libraries contained 88,694 and 88,698 SAGE tags respectively. For comparison, the corresponding number of SAGE tags found in cultured human umbilical vein endothelial cells (HUV-EC), human dermal microvascular endothelial cells (HMEC), and non-endothelial cell lines (Cell Lines) are shown. The HUV-EC SAGE library contained 280,000 tags and the HMEC library 111,000 tags. Non-endothelial cell lines consisted of 1,810⁶ tags derived from a total of 14 different cancer cell lines including colon, breast, lung, and pancreatic cancers, as well as one non-transformed keratinocyte cell line, two kidney epithelial cell lines, and normal monocytes. Tag numbers for each group were normalized to 100,000 transcripts. A 'Description' of the gene product corresponding to each tag is given, followed by alternative names in parenthesis. The sequence CATG precedes all tags and the 15th base (11th shown) was determined as previously described by Valculescu et al. (Nat Genet 1999 Dec;23(4):387-8).

no.	Tag Sequence	N-EC's	T-EC's	HUV-EC	HMEC	Cell Lines	Description
1	CATATCATTA	247	501	130	87	2	angiomodulin (ANG, IGFBP-7, IGFBP-rP1, Mac25, TAF)
2	TGCACCTCAAG	328	141	0	0	0	hevin
3	TTGCACCTT	165	84	181	115	4	connective tissue growth factor (CTGF, IGFBP-rP2)
4	CCCTTGTCGG	131	104	1	1	0	ESTs
5	TTCTGACTT	73	151	2	14	1	collagen, type VI, alpha 1
6	ACCATGGAT	102	67	0	0	2	interferon induced transmembrane protein 1 (9-27, Lau 13)
7	ACACTGCTTC	104	44	60	62	2	guanine nucleotide binding protein 11
8	TTCTGCTCTG	71	67	118	72	0	von Willebrand factor
9	TCCTGGGAGA	68	68	3	13	3	cysteine-rich protein 2 (CRP-2, ESP-1, SmLIM)
10	TAATCCTCAAG	28	106	34	16	1	collagen, type XVIII, alpha 1
11	ATGTCTTTCT	68	65	17	17	3	insulin-like growth factor-binding protein 4
12	GGGATTAAAGC	40	67	30	14	2	CD148 (S-Endo 1, PTH12, Muc18, MCAM, Mel-CAM)
13	TTAGTGTGTA	38	69	9	13	0	SPARC (osteonectin, BM-40)
14	TTCTCCCAAT	20	88	16	84	2	collagen, type IV, alpha 2
15	GTGCTAAGCGG	24	74	0	10	2	collagen, type VI, alpha 2
16	GTTTATGGATA	35	68	11	11	1	matrix Gla protein (MGP)
17	CCCTTCACAC	52	33	0	0	0	ESTs, Weakly similar to HPR11-7 protein
18	TGTTCTGGAGA	58	27	18	56	2	gap junction protein, alpha 1, 43kD (connexin 43)
19	AAGATCAAGAT	34	50	2	4	1	actin, alpha 1, skeletal muscle / actin, alpha 2, smooth muscle, aorta
20	TCTCTGAGCAT	32	48	0	0	0	aggrecanase 1 (metalloproteinase with thrombospondin type 1 motifs, 4)
21	CAGGTTTCATA	22	56	0	0	0	small inducible cytokine subfamily 8 (Cys-X-Cys), member 14 (BRACQ)
22	GCACAAATCT	43	26	6	22	0	calcitonin receptor-like receptor activity modifying protein 2
23	ACTCTGTGGCC	45	23	0	0	0	calcitonin receptor-like receptor activity modifying protein 3
24	CTTCTGGATA	13	54	12	0	0	cell division cycle 42 (GTP-binding protein, 25kD)
25	CAACAAATA	42	25	13	6	0	ESTs

G1

26	ACCGGGGCGCG	50	15	0	0	0	0	tetranectin (plasminogen-binding protein)
27	GGAAGCTAAGT	35	27	0	5	1	1	osteoblast specific factor 2 (fascilin 1-like)
28	GCAATTAAACC	38	21	0	3	0	0	soluble carrier family 21 (prostaglandin transporter), member 2
29	GATAACTACAT	18	35	4	4	0	0	angiomodulin (ANG, IGFBP-7, IGFBP-rP1, Mac25, TAF)
30	TATGAGGGTAA	19	30	40	2	0	0	regulator of G-protein signalling 5
31	CCACGGGGATTC	10	39	0	0	0	0	collagen, type III, alpha 1
32	TTTACAAAGAG	28	21	0	1	1	1	carboxypeptidase E
33	CCCAGTAAGAT	22	25	0	18	1	1	cysteine and glycine-rich protein 2 (LIM domain only, smooth muscle)
34	ACAAAGCATTT	28	20	0	14	1	1	Human insulin-like growth factor binding protein 5 (IGFBP5) mRNA
35	GCCTGTCCCTC	8	38	22	11	0	0	ESTs / biglycan
36	TACTTTATAAG	25	21	1	1	0	0	metalloproteinase with thrombospondin type 1 motif (ADAMTS1, METH-1)
37	TGTTTAATACA	15	29	2	1	1	1	ESTs / erythrocyte membrane protein band 4.1-like 2
38	GTCCCTGCCTT	18	25	1	1	0	0	glutathione S-transferase M2 (muscle)
39	GAGCCATCATA	21	21	2	2	1	1	ESTs / GTP-binding protein overexpressed in skeletal muscle
40	GCCCTACAGT	26	13	2	3	0	0	ESTs / KIAA0821 protein
41	GCTAACCCCTG	7	31	0	1	0	0	ESTs
42	ATCACACAGCT	19	18	0	0	0	0	thyroid and eye muscle aipantigen D1 (84kD)
43	ACAAGTACTGT	18	19	38	27	0	0	cadherin 5, VE-cadherin (vascular epithelium)
44	TCACCGTGGAC	20	17	0	1	0	0	selectin P (granule membrane protein 140kD, antigen CD82)
45	ACATTCCAACT	18	18	0	1	1	1	tissue inhibitor of metalloproteinase 3
46	GAGCCTGGATA	6	29	0	0	0	0	chondroitin sulfate proteoglycan 4 (melanoma-associated)
47	GGCACTCCTGT	22	13	19	12	0	0	ESTs
48	TCACAGCCCCC	20	15	8	5	0	0	ESTs
49	TGCCAGGTGCA	10	23	0	1	0	0	albumin
50	TGGGAACCTG	11	22	0	1	1	1	eukaryotic translation initiation factor 4 gamma, 1
51	TTTCATCCACT	20	13	0	2	0	0	ESTs, KIAA0382 protein
52	AACAGGGGCCA	15	18	0	0	1	1	interferon, alpha-inducible protein (clone IFI-8-16)
53	ACTGAAAGAAG	6	28	0	0	1	1	complement component 1, s subcomponent
54	ACCGTTCTGTA	8	24	10	6	0	0	transcription factor 4
55	ATACTATAATT	25	6	12	0	0	0	ESTs
56	TTTGATAGAA	17	15	4	5	1	1	hect domain and RLD 2
57	GTAATGACAGA	20	11	1	1	1	1	stanniocalcin
58	AATAGGGGAAA	13	19	4	1	0	0	ESTs, KIAA1075 protein
59	GTGCTACTTCT	5	25	2	18	0	0	collagen, type IV, alpha 1
60	CCGGCCCTCC	6	24	0	0	1	1	peanut (Drosophila)-like 2
61	TTGAATTTGTT	19	10	1	1	0	0	RNA-binding protein gene with multiple splicing
62	CGAGAGTGTGA	22	8	0	0	0	0	ESTs
63	CCCTGTTTCAGC	14	15	38	24	0	0	tyrosine kinase with IgG and EGF homology domains (Tie)

64	CAGATGGAGGC	18	10	1	9	0	ESTs
65	AGGCTCCTGGC	8	20	0	0	0	ESTs
66	TCTGCTTCTAG	20	8	40	15	0	ESTs
67	GGCTTAGGATG	18	9	10	14	0	ESTs
68	GGTTGTTGCCG	6	21	0	0	1	ESTs
69	ACAAGTACCCA	5	22	4	5	0	P311 protein
70	CTTCTCTTGAG	18	9	1	4	1	basic transcription element binding protein 1
71	GCTAATAATGT	10	17	0	2	0	KIAA1077 protein
72	TGTGCTTTTTT	10	15	1	4	0	KIAA0758 protein / protein kinase, cAMP-dependent, catalytic, alpha
73	CATCAGGATC	17	8	0	1	0	Interleukin 1 receptor, type I
74	GCAGCAGCAGC	8	18	0	2	0	T-box 2
75	TGACTGTATTA	13	11	0	0	0	ESTs / amine oxidase, copper containing 3 (vascular adhesion protein 1)
76	GAATGCTCTTG	6	18	0	11	0	gap junction protein, alpha 4, 37kD (connexin 37)
77	GTAGTTCTGGA	18	6	0	5	0	ESTs, clone 23698 mRNA
78	TCCCCTCTCTC	6	17	0	0	0	periodontal ligament fibroblast protein
79	GGGCAGTGGCT	6	18	12	5	0	ESTs, DKFZP688B0621 protein
80	AAATATGTGTT	19	4	13	3	0	ESTs
81	GTCATTTTCTA	11	11	10	2	0	transcription factor 8 (represses Interleukin 2 expression)
82	CTCTCCAAACC	14	8	0	0	0	complement component 1 inhibitor (angioedema, hereditary)
83	TTAATGTGTAA	4	18	0	0	0	guanylate cyclase 1, soluble, beta 3
84	TCAAGCAATCA	13	9	0	1	0	ESTs
85	GAAGACACTTG	15	7	1	0	0	ESTs
86	GGTAGGGTGA	6	15	0	0	1	Integrin, alpha 7
87	TGGAACAGTGA	10	10	10	5	0	ESTs
88	GAGTGGGTACC	10	9	0	0	0	ESTs
89	GTCAGGGTCCC	13	7	0	9	0	decidual protein induced by progesterone
90	GTCAGTCACTT	14	6	4	1	0	halcy (Drosophila)-homolog
91	AGCAGAGACAA	14	6	1	10	0	nauretic peptide receptor A - guanylate cyclase A
92	AGCGATGGAGA	9	10	0	0	0	ESTs
93	CGTGGGGTGTA	9	10	17	3	0	

TEM's complete web table

Table 2. SAGE tags elevated in tumor endothelium. The top 46 tags with the highest tumor EC (T-EC's) to normal EC (N-EC's) tag ratios are listed in descending order. To calculate tag ratios, a value of 0.5 was assigned in cases where zero tags were observed. The SAGE libraries are the same as those listed in Table 1. Tag numbers for each group were normalized to 100,000 transcripts. A 'Description' of the gene product corresponding to each tag is given, followed by alternative names in parentheses. †: multiple tags for this gene are due to alternative polyadenylation sites.

no.	Tag Sequence	N-EC's	T-EC's	HUVEC	HMVEC	Cell Lines	Description
1	GGGGCTGCCCA	0	28	0	2	0	ESTs, similarity to thrombospondin
2	GATCTCCGTGT	0	25	0	0	0	ESTs, similarity to rat Rhesus ras-related protein
3	CATTTTATCT	0	23	0	0	0	ESTs
4	CTTCTTTGAG	0	22	6	20	1	regulated in glioma-like 7-1 (Dkk-3/REIC)
5	TATTAAGTCTC	0	21	1	3	1	ESTs, similarity to JNK interacting protein-3a
6	CAGGAGACCCC	0	18	2	0	0	MMP-11 (stromelysin 3)
7	GGAAATGTCAA	1	31	53	22	1	MMP-2 (gelatinase A, 72kD type IV collagenase)
8	CCTGGTTCAGT	0	15	0	0	0	ESTs
9	TTTTAAGAAC	0	14	1	4	0	ESTs
10	TTTGGTTTCC	5	139	0	16	0	collagen, type I, alpha 2, transcript A'
11	ATTTGTATGA	0	13	4	8	0	nidogen (entactin)
12	ACTTTAGATGG	1	23	0	15	0	collagen, type VI, alpha 3
13	GAGTGAGACCC	3	63	0	0	1	Thy-1 cell surface antigen
14	GTACACACACC	0	10	0	0	0	ESTs / cystatin S
15	CCACAGGGGAT	2	38	0	2	1	collagen, type III, alpha 1
16	TTAAAAGTCAC	1	19	1	3	1	ESTs
17	ACAGACTGTTA	4	74	0	0	0	ESTs, similarity with sea squirt nidogen
18	CCACTGCAACC	1	18	0	1	0	ESTs, similarity with homeobox protein DLX-3
19	CTATAGGAGAC	1	18	1	1	0	collagen, type I, alpha 2, transcript B'
20	GTTCCACAGAA	0	9	0	3	0	ESTs / pregnancy specific beta-1-glycoprotein 1
21	TACCACCTCCC	0	9	4	1	1	endo180 lectin
22	GCCCTTTCTCT	1	17	3	1	2	collagen, type I, alpha 1
23	TTAAATAGCAC	2	33	0	4	0	ESTs, DKFZP434G162 protein
24	AGACATACTGA	1	16	1	0	0	bone morphogenetic protein 1 (metalloprotease)
25	TCCCCCAGGAG	1	16	0	0	0	silt (Drosophila) homolog 3 (MEGFS)
26	AGCCCAAAGTG	0	8	0	0	0	KIAA0672 gene product
27	ACTACCATAAC	0	8	0	0	0	
28	TACAAATCGTT	0	8	0	0	0	

See table 2 from paper for G162dr G2

all 63

29	TTGGGTGAAA	0	8	0	0	0	0	ESTs
30	CATTATCCAAA	0	8	0	0	0	0	Integrin, alpha 1
31	AGAAACCCACGG	0	8	2	7	0	0	collagen, type IV, alpha 1
32	ACCAAACCCAC	0	8	0	3	0	0	
33	TGAAATAAAC	0	8	3	1	1	0	ESTs
34	TTTGGTTTCC	1	15	0	0	0	0	ESTs
35	GTGGAGACGGA	1	15	1	2	1	0	ESTs
36	TTTGTGTTGTA	1	14	2	0	0	0	collagen, type XII, alpha 1
37	TTATGTTTAAT	3	39	0	0	0	1	lumican
38	TGGAATGACC	15	179	0	40	0	0	ESTs / collagen, type I, alpha 1
39	TGCCACACAGT	1	13	0	2	0	0	transforming growth factor, beta 3
40	GATGAGGAGAC	3	35	0	18	1	0	collagen, type I, alpha 2, transcript C1
41	ATCAAAGGTTT	2	23	0	0	0	0	ESTs, DKFZp584O222 mRNA
42	AGTCACATAGT	1	11	2	0	0	0	cell division cycle 42 (GTP-binding protein)
43	TTCGGTTGGTC	4	45	0	19	0	0	
44	CCCCACACGGG	2	21	0	0	0	0	ESTs
45	GGCTTGCCTTT	1	10	0	10	0	0	
46	ATCCCTTCCCG	1	10	1	0	0	0	peanut-like protein 1

Table 3. Detection of transcripts in various tumor types by RT-PCR and In situ hybridization (ISH). The "+" sign indicates the presence of a robust RT-PCR product or strong positive staining of vessels by In situ hybridization. The "-" sign indicates an undetectable signal by In situ hybridization or an absent or barely detectable transcript by RT-PCR. The "+/-" sign indicates a very weak signal in a limited number of vessels by In situ hybridization.

	TEM1	TEM3	TEM4	TEM5	TEM7	TEM8	TEM9	vWF	Hevin
RT-PCR	Colon Nor.	-	-	-	-	-	-	+	ND
	Colon Tum.	+	+	+	+	+	+	+	ND
ISH	Colon Nor.	-	-	-	-	-	-	+	+
	Colon Tum.	+	+	+	+	+	+	+	+
	Liver Met.	+	+/-	+	+	+	+	+/-	ND
	Lung Tum.	+	ND	+	+	+	+	+	+
	Brain Tum.	+	ND	ND	+	ND	ND	+	+
	Corpus Lut.	+	+	+	+	-	+	+	+
	Wound	+	ND	+	ND	+/-	ND	+	+

* hevin was localized to both endothelial cells and malignant cells in brain tissue.
 ND: not determined.

www.sagenet.org/langtable3.htm (to be posted upon publication)

4

Table 3. SAGE tags elevated in normal endothelium. The top 46 tags with the highest normal EC (N-EC's) to tumor EC (T-EC's) tag ratios are listed in descending order. To calculate tag ratios, a value of 0.5 was assigned in cases where zero tags were observed. The SAGE libraries are the same as those listed in Table 1. Tag numbers for each group were normalized to 100,000 transcripts. A 'Description' of the gene product corresponding to each tag is given, followed by alternative names in parenthesis.

no.	Tag Sequence	N-EC's	T-EC's	HUVEC	HMVEC	Cell Lines	Description
1	TCTCAGCTCT	26	0	0	0	0	mucosal vascular addressin cell adhesion molecule 1
2	CTAGCGTTTT	19	0	4	14	0	serum deprivation response (phosphatidylserine-binding protein)
3	GTGGCTGACG	18	0	1	0	0	ESTs / Intercellular adhesion molecule 4
4	CTCTTAAAAA	34	1	1	0	0	small inducible cytokine subfamily A (Cys-Cys), member 14
5	TGGGAAGAGG	16	0	3	4	1	ESTs
6	GTTTAAGGAT	16	0	0	0	0	ESTs
7	CTTTGTTTGG	15	0	56	32	1	endothelin 1 / ribosomal protein L27
8	ATTGCCAATC	14	0	0	4	0	TU3A protein
9	TGTTGAAAAA	21	1	1	0	0	selectin E (endothelial adhesion molecule 1)
10	ACAAAAAGGC	21	1	0	6	0	TU3A protein
11	AAGATGCACAC	21	1	1	1	1	phosphodiesterase 1 - nucleotide pyrophosphatase 2 (autotaxin)
12	GTAGAGGAAA	10	0	0	9	0	platelet/endothelial cell adhesion molecule (CD31 antigen)
13	TTGTTCAAGG	10	0	0	1	0	ESTs
14	CTCTTCAAAAA	19	1	1	0	0	ESTs / small inducible cytokine subfamily A, member 14
15	TATTAAAAATA	18	1	8	9	1	transforming growth factor, beta receptor II (70-80kD)
16	GAATTCACCA	9	0	1	14	0	ESTs
17	AAGGAGAACT	9	0	0	0	0	small inducible cytokine subfamily A, member 14
18	AATATCTGAC	9	0	2	2	2	active BCR-related gene
19	TCAGTGACCAG	17	1	4	7	2	protein kinase C eta
20	GCAAAGTGCC	32	2	1	5	0	ESTs
21	TAAATACTTG	8	0	2	0	0	ESTs (2 unigene clusters)
22	GTCACATAAT	8	0	1	0	0	ESTs
23	ATAACCTGCA	8	0	0	0	0	signaling lymphocytic activation molecule
24	TGCATCTGTGC	46	3	1	1	0	ESTs / glycogenin 2
25	TAAAGGCACA	15	1	4	3	0	LIM binding domain 2
26	GACCGCGGCT	73	5	11	7	0	claudin 5
27	ACTCCGGTGT	14	1	0	8	0	ESTs

28	CTTCTCACCT	27	2	3	1	0	GTP-binding protein
29	TCGTGCTTTG	13	1	0	0	0	ESTs
30	GAGCAGTGCT	13	1	4	2	1	feline sarcoma viral (v-fes) - Fujinami avian sarcoma viral (v-fps) homolog
31	CTCTAAAAAA	10	1	0	1	0	ESTs
32	GAAACCCCGT	10	1	0	0	1	phospholipase C, beta 4
33	AACACAGTGC	10	1	7	15	1	ESTs

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